



# ARCHIVES OF OPHTHALMOLOGY

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JANUARY 1949

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH  
DEARBORN STREET, CHICAGO 10, ILLINOIS ANNUAL SUBSCRIPTION, \$10 00





## CONTENTS

---

	PAGE
Beta Radiation Therapy. A. D RUEDEMANN, M.D, DETROIT .. . . .	1
Motor Block of Extraocular Muscles by Deep Orbital Injection. HAROLD GIFFORD JR, M D, OMAHA... .. .	5
Responses to the Ishihara Test for Color Perception J B NOLASCO, M D, MANILA, PHILIPPINES, AND DEOGRACIAS RODIL, M D, CHAMPAIGN, ILL. .... .	20
Interstitial Keratitis and Vestibuloauditory Symptoms Following Vaccination. EMANUEL ROSEN, M D, NEWARK, N J.... .	24
Retinoblastoma (Retinal Glioma) Cured by Radon Seeds: Report of a Case. JOSEPH WALDMAN, M D, AND C E G. SHANNON, M D, PHILADELPHIA .... .	32
Mydriatics: A Clinical Observation. J B FELDMAN, M D, PHILADELPHIA	42
Malignant Retrobulbar Neuritis. ADALBERT FUCHS, M D., SHANGHAI, CHINA .. . . .	60
Technic of Goniotomy for Congenital Glaucoma. OTTO BARKAN, M.D, SAN FRANCISCO . .... .	65
Use of Propionates in Ophthalmology: A Preliminary Report. FREDERICK H THEODORE, M D, NEW YORK .. . . .	83
ABSTRACTS FROM CURRENT LITERATURE . . . . .	95
BOOK REVIEWS..... .	109
DIRECTORY OF OPHTHALMOLOGIC SOCIETIES .. . . .	111

THE ARCHIVES OF OPHTHALMOLOGY is published by the American Medical Association to continue the *Archives of Ophthalmology* founded by Herman Knapp in 1869 and to provide American ophthalmologists with a publication devoted not only to original contributions in the field of ophthalmology but to a survey of the ophthalmic literature and a review of the transactions of ophthalmic societies

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# CONTENTS

---

	PAGE
<b>Role of Inheritance in Glaucoma.</b> ADOLPH POSNER, M D, AND ABRAHAM SCHLOSSMAN, M D, NEW YORK	125
<b>Experimental Studies of Inclusion Blennorrhoea Isolation of a Virus</b> ALSON E BRALEY, M D, NEW YORK . . .	151
<b>Use of Phenylephrine Hydrochloride (Neo-Synephrine Hydrochloride®) in Ophthalmology</b> PARKER HEATH, M D, BOSTON, AND C W GEITER, M D, NORTH KANSAS CITY, MO	172
<b>Juxtapapillary Hemangioendothelioma of the Retina Report of a Case</b> BENJAMIN F SOUDERS, M D, Sc D (MED), READING, PA	178
<b>Scleromalacia Perforans: Report of a Case</b> MELVIN HARBATER, M D, MANHASSET, N Y .	183
<b>Congenital Ptosis: A Classification of Two Hundred Cases.</b> RAYNOLD N BERKE, M D, HACKENSACK, N J	188
<b>OPHTHALMOLOGIC REVIEWS</b>	
Intraorbital Tumors. ARNOLD W FORREST, M D, NEW YORK	198
<b>ABSTRACTS FROM CURRENT LITERATURE</b>	233
<b>CORRESPONDENCE.</b>	
Muscle Schemas JOSEPH I PASCAL, M D, NEW YORK	245
<b>NEWS AND NOTES</b>	246
<b>BOOK REVIEWS</b>	249

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## CONTENTS

	PAGE
Persistence and Hyperplasia of Primary Vitreous, Retrolental Fibro- plasia—Two Entities. ALGERNON B. REESE, M D, NEW YORK . . .	527
Histopathologic Aspects of Retrolental Fibroplasia. BERTHA A KLIEN, M D, CHICAGO....         .....	553
Divergence Insufficiency as a Practical Problem. L WESTON OAKS, M D ,' PROVO, UTAH         . . . . .	562
An Early Photograph of von Helmholtz with Explanatory Letter. JOSEPH C AUB, M.D, BOSTON                 .	570
Production of Cataract in Rats by Beta-Tetralol and Other Deriva- tives of Naphthalene. O GARTH FITZHUGH, PH D, WASHINGTON, D C, AND WILHELM H BUSCHKE, M D, BALTIMORE	572
Use of Antihistaminic Drugs in Control of Atropine Dermatitis and Conjunctivitis. F BRUCE FRALICK, M D, AND ROBERT D KIESS, M D, ANN ARBOR, MICH. ....	583
Choroidal Metastasis of a Testicular Chorionic Epithelioma: Report of a Case. GEORGE K KAMBARA, M D, LOS ANGELES. .	587
Voluntary Dissociation of the Accommodation and the Convergence Faculty: Two Observations C KEITH BARNES, M D, FORT WORTH, TEXAS ..... ..	599
A Surgical Approach to the Inferior Oblique Muscle. WALTER F. JOHNSON, M D, NEW YORK ...         .	607
Studies of the Eye with Radiosodium Autographs LUDWIG VON SALLMANN, M D , TITUS C EVANS, PH D, AND BEATRICE DILLON, M A , NEW YORK .         .....	611
Treatment of Pediculosis Ciliaris with Anticholinesterase Agents: Report of a Case. DAVID G COGAN, M D, AND W MORTON GRANT, M D, BOSTON         ..         .	627
Intravitreal Use of Streptomycin. ROBERT E SHOEMAKER, M D, ALLEN- TOWN, PA         . . . . .	629
CLINICAL NOTES:	
A Simplified Perimeter of Wall Type. ANTHONY AMBROSE, M D , NEWARK, N J         .	633
NEWS AND NOTES ..         .	637
ABSTRACTS FROM CURRENT LITERATURE .         .	639
BOOK REVIEWS         .	653

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CHICAGO 10

# CONTENTS

---

	PAGE
Blood Groups and Effects of Roentgen Irradiation in Retroental Fibroplasia. THOMAS O PAUL, M D, BIRMINGHAM, ALA	659
Differential Diagnosis of Boeck's Sarcoidosis. Report of Ten Cases with Ocular Involvement. BYRON L GIFFORD, M D, AND ARLINGTON C KRAUSE, M D, CHICAGO ..	667
Ocular Findings in Three Hundred and Twenty-Three Patients with Schizophrenia. A Preliminary Report MARTIN COHEN, M D, NEW YORK . . . . .	697
Reserve Accommodation. HARRY EGGERS, M D, NEW YORK .	701
Supposed Torsion of the Eye Around the Visual Axis in Oblique Directions of Gaze PROF M MÁRQUEZ, M D, MÉXICO, D F, MEXICO	704
Neurofibromatosis Associated with Tumors of the Optic Papilla: Report of a Case J GOLDSMITH, M D, NEW YORK. .	718
Contact Lens Electrode for Iontophoresis. PAUL TOWER, M D, LOS ANGELES 1... . . . .	730
Congenital Cyst of the Vitreous: Report of a Case. J. V. CASSADY, M D, SOUTH BEND, IND . . . . .	734
<b>OPHTHALMOLOGIC REVIEWS.</b>	
Metabolism of the Cornea T D DUANE, M D, IOWA CITY .	736
<b>NEWS AND NOTES . . . . .</b>	<b>750</b>
<b>OBITUARIES:</b>	
JOHN ELMER WEEKS, M D . . . . .	752
<b>ABSTRACTS FROM CURRENT LITERATURE .. . .</b>	<b>755</b>
<b>BOOK REVIEWS . . . . .</b>	<b>765</b>
<b>GENERAL INDEX . . . . .</b>	<b>767</b>



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## BETA RADIATION THERAPY

A. D. RUEDEMANN, MD  
DETROIT

### METHOD OF APPLICATION

**I**N THE treatment of certain diseases of the eye, beta radiation from decay products of radium is made use of by means of a beta ray applicator

Radon is sealed in a small glass sphere (fig 2, *R*) in the applicator. The diameter of this sphere is about 4 mm and the thickness of the wall about 0.1 mm. The glass sphere is inserted into a thin copper capsule (fig 2, 2, 3), and a spring holds it tightly against the open window (at 2) of the capsule. The metal capsule with sphere is inserted into an open end brass holder (1, 4), with a wall 2 mm thick. On contact of the open window with the tissue to be treated, only the thin glass window separates the tissue from the radon. Alpha rays are absorbed in the glass window. Radiation transmitted through this window consists of about 97 per cent beta rays and 3 per cent gamma rays.

*Dosage of Beta Radiation*—The dosage usually used with the beta ray applicator for contact therapy is 5,000 millicurie seconds. For a 250 millicurie (measured for emission of gamma rays) radon bulb, the treatment time is, therefore, twenty seconds. This dose corresponds to about 600 r. It will produce pronounced erythema of the skin within three days.

*Protection in Beta Radiation Therapy*—Distance from the source of radiation is the best protection. Since this beta ray applicator also emits gamma rays, it is equipped with a long handle, and a double length tongue blade is used to hold the lid during treatment. When not in use, the applicator is placed in a lead container with walls 2 inches (5 cm) thick.

The speculum must be adjusted before the applicator is placed on the lesion. Should it slip during treatment, the applicator must be removed while it is adjusted. The glass window of the beta ray applicator must be pointed only toward lesion to be treated, and never toward any other part of the patient or toward the ophthalmologist.

When the ophthalmologist is holding the beta ray applicator, filled with 250 millicuries of radon, his fingers will receive the daily tolerance dose of 0.1 r within five minutes. This would permit his giving about ten treatments, allowing for a treatment time of twenty seconds and time for handling between treatments, provided he is not exposed to any other type of radium or roentgen radiation. The treatment time must be accurately determined with the stopwatch.

*Factors in Therapy*—1 Treatment should be either by direct contact or by spray radiation. 2 The time of treatment varies according to the type of lesion, the strength of the tube and the reaction to treatment. 3 The time factor is important in treatment of corneal lesions, it is difficult for children and for some adults to hold still for over twenty-five seconds. Use of a stronger tube with a short time factor is advisable. 4 Age is not a factor, this treatment

has been used with infants as young as 6 months 5 The only discomfort to the patient is his own fear 6 As a measure of economy, a number of patients should be arranged for treatment at one time This reduces the cost per patient and saves time 7 Separate record cards are kept for instant reference

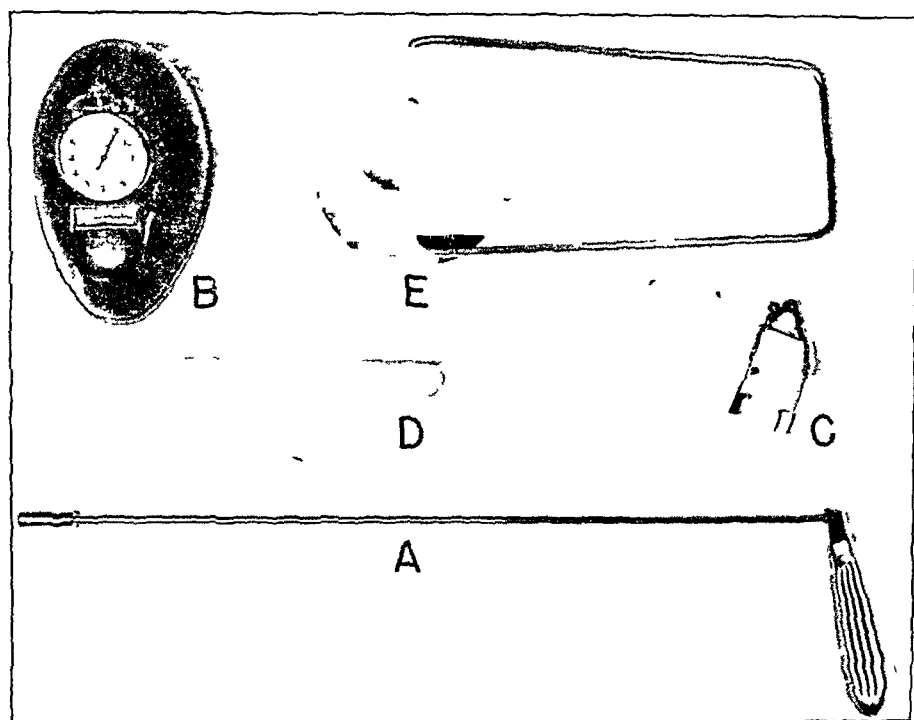


Fig 1—Beta ray applicator (*A*), 40 cm in length *B* is the stopwatch, *C*, the eye speculum, *D*, the double length tongue blade, and *E*, the lead box

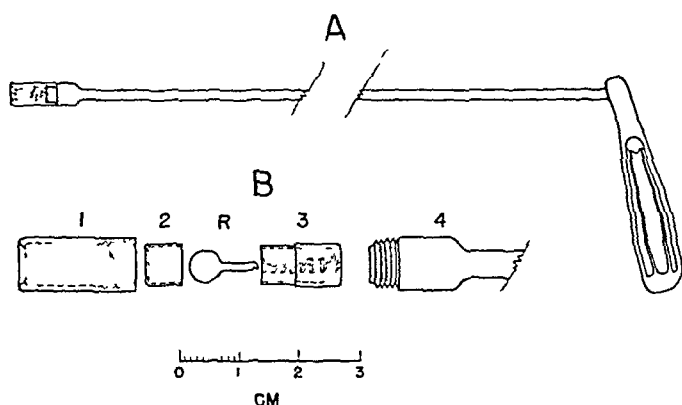


Fig 2—Drawing of the beta ray applicator *A* shows the beta ray applicator assembled, *B*, details of the applicator, as follows *R*, radon-filled thin glass bulb, 2 and 3, thin metal capsule with open window at 2, 1 and 4, heavy brass holder with open window at 1

#### CONDITIONS SUITABLE FOR IRRADIATION

The conditions which are suitable for beta radiation therapy are overgrowths of the lid, of minor importance to vision but of major

importance to appearance. Large, infiltrating growths suggestive of carcinoma should be excised and treated with gamma rays of radium or by roentgen radiation. When the growth is small, shallow or difficult to excise, application of the beta radiation of radium is the treatment of choice. Although beta rays are of low voltage, only one-half a given surface dose is absorbed in 2 mm of tissue, and all minor lesions are easily and successfully treated. Small malignant growths, to which it is difficult to apply gamma or roentgen rays, can be given one or two applications, and they will be destroyed with little or no loss of lashes. Beta radiation can be used as well for small angiomas in babies. The time of application is short, and, if a simple holding technic is used, no anesthetic is required. In treatment of other cutaneous lesions around the eyes, use of beta radiation is suggested, as it leaves no discoloration of the skin or depigmentation and there is no tendency to a deep bronzing effect.

*Vernal Conjunctivitis*—Large polypoid masses are treated as follows

- 1 If the polyps are of long standing and fibrotic, they should be excised.

- 2 Gamma radiation may be given. The eye must be carefully screened with lead plates, the lid everted and the applicator directly applied. This therapy gives prompt relief but may need to be repeated. Cold compresses and irrigation minimize edema and reaction.

- 3 The larger polyps having been excised or reduced in size, beta radiation can be directly applied to the individual polyps, especially those along the superior aspect of the tarsus. Mild catarrhal lesions may be treated with spray radiation. The effect is prompt and lasting. Individual polyps and small areas are easily reached.

- 4 Except in urgent cases, in which use of gamma radiation is advisable, beta radiation can be easily and quickly applied in children. The end results are similar to those of gamma rays.

- 5 The long applicator, to evert the lower lid, and the double length tongue blade (page 2) are safety aids in the therapy.

*Conjunctival Lesion*—Small lesions on the bulbar conjunctiva can be treated directly with beta radiation. Small, superficial growths require but one application, rarely two, by direct contact. Vascular growths are more resistant but can be treated by direct contact. Spray radiation is of value and is given by moving the applicator over the area to be treated, so that the entire area receives a small amount of this radiation and the applicator is not in contact with one area for any period of time. Enlargement of the caruncle, enlarged pinguecula and beginning pterygium are well treated by direct application, as are small pseudopterygia. Large true pterygia and large pseudopterygia are treated with spray radiation over the corneal portion combined

with direct application along the limbal portion. Recurring pterygia having interstitial vascular trunks require contact irradiation over most of the extent to eliminate deep vascularization. Marginal carcinoma is satisfactorily treated by direct contact.

*Corneal Lesions*—Deep or superficial keratitis, whether due to tuberculosis, syphilis or brucellosis, is known to have been successfully treated with beta radiation. General therapy should be directed to the etiologic factor. Corneal nebulas following ulcer, trauma or allergy are usually cleared, with little residual scarring. Maculas of the cornea can be substantially reduced in area and sufficiently cleared so that patients are able to carry on without corneal transplantation. Vascularized leukoma can be treated, so that the hazard of vascularization of a corneal transplant is lessened. Corneal transplants with a tendency to vascularization can be treated to prevent complete vascularization. Diminution in the area of corneal scarring and reduction in density are major factors in beta radiation therapy.

#### SUMMARY

There is a twofold hazard in the use of radiation therapy (1) to the patient, due to overdosage, faulty application or severe reaction, and (2) to the ophthalmologist. The value of radiation is stressed because of its usefulness in treatment of so many conditions previously supposed to be incurable. Use of roentgen, gamma or beta radiation offers a valuable therapeutic adjunct in ophthalmology. To date, there has been no definite evidence of injury to the eye with beta radiation. In several cases of severe corneal leukoma, excessive treatment with beta radiation produced small perforating ulcers and enucleation was necessary. Roentgen and gamma radiation therapy may produce cataract and injure the retina permanently. It is possible to use the various forms of radiation in a single case. Care must be taken to allow for subsidence of reaction if such a procedure is indicated. Photographs and drawings are valuable aids in progress notes.

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## MOTOR BLOCK OF EXTRAOCULAR MUSCLES BY DEEP ORBITAL INJECTION

HAROLD GIFFORD Jr, M D  
OMAHA

THE VALUE of retrobulbar anesthesia has been appreciated by the majority of ophthalmic surgeons ever since Elschnig's<sup>1</sup> work was published, in 1925. He pointed out that this method of anesthesia produced a lowering of the intraocular tension, as well as anesthesia. Elschnig,<sup>2</sup> Grósz,<sup>3</sup> Dunphy,<sup>4</sup> Greenwood and Grossman,<sup>5</sup> my brother, Sanford Gifford,<sup>6</sup> and others, all expressed the belief that retrobulbar anesthesia reduced the percentage of cases of loss of vitreous in cataract extractions. In my study<sup>7</sup> on loss of vitreous, I demonstrated that the extraocular muscles were capable of producing the massive losses that occur in about 10 per cent of cases of loss of vitreous. The tonus of these muscles also contributes to the production of the smaller losses of vitreous. I stated the belief that a more complete motor block of the extraocular muscles would prevent the massive loss of vitreous and reduce the smaller losses to a minimum. A review of the literature revealed little on the production of motor block. In the latest edition of his text, Pitkin<sup>8</sup> gives a definite plan for obtaining both a motor and a sensory block. This reads well and is accompanied with excellent

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From the Departments of Ophthalmology and Anatomy, the University of Nebraska College of Medicine

Read before the Section on Ophthalmology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948

1 Elschnig, A. Extraction of Senile Cataract in Capsule, *Am J Ophth* **8** 355-361, 1925

2 Elschnig, A. Hilfsverfahren bei der Alterstarextraction, *Arch f Augenh* **98** 300-305, 1927

3 Grosz, E. L'extraction de la cataracte d'après 15,000 operations, *Arch d'opht* **53** 161-165, 1936

4 Dunphy, E. H. Loss of Vitreous in Cataract Extraction, *J A M A* **89** 2254-2257 (Dec 31) 1927

5 Greenwood, A., and Grossman, H. P. An Analysis of 1,343 Intracapsular Cataract Extractions, Forty-Eight Operations Following Verhoeff's Method *Tr Am Ophth Soc* **33** 353-361, 1935

6 Gifford, S. R. Prevention of Complications in the Cataract Operation, *Illinois M J* **68** 243-245, 1935

7 Gifford, H., Jr. A Study of Vitreous Pressure in Cataract Surgery, *Tr Am Ophth Soc* **44** 435-492, 1946

8 Pitkin, G. P. Conduction Anesthesia in General Surgery, Philadelphia, J. B. Lippincott Company, 1946, pp 333 and 374

illustrations, but in my hands the method has failed to produce the desired results

After I had measured 50 skulls and dissected many orbits in the cadaver with this problem in mind, the reasons for the poor results became obvious. First, the average distance of the anterior edge of the optic foramen from the inferior orbital margin was found to be 5.02 cm (fig 1). In the smallest skull the distance was 4.5 cm, and in

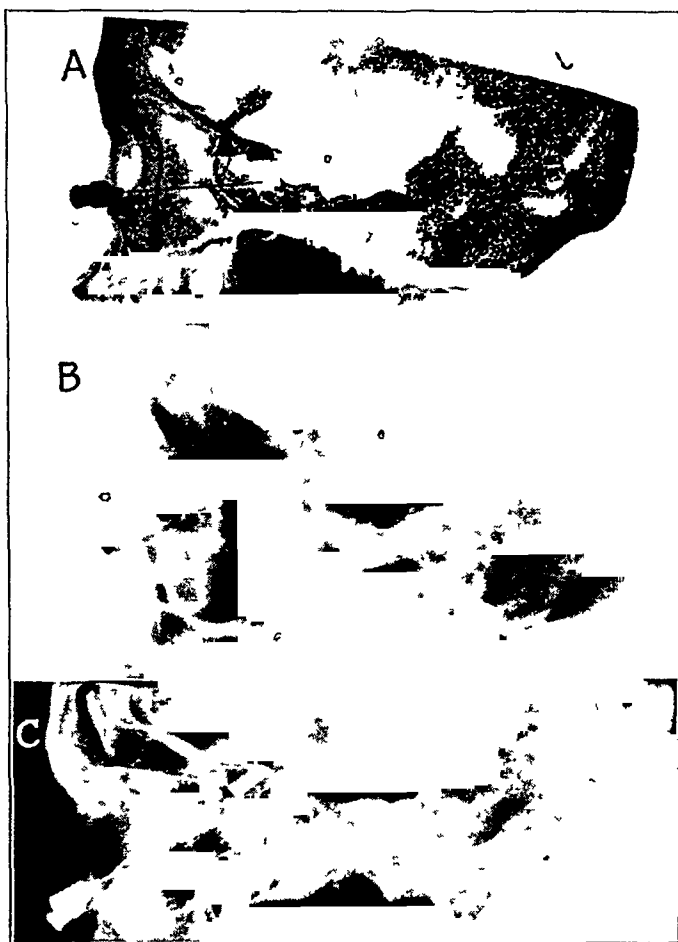


Fig 1—Shortest orbit, 5.5 cm, with the 5 cm needle in place, B, longest orbit, 5.8 cm, with the 5 cm needle in place, C, average orbit, 5.02 cm, with 5 cm and 3.5 cm needles in place

the largest, 5.8 cm. It was obvious that the usually recommended 3.5 cm needle could not possibly block the motor nerves as they enter the orbit. Second, the ciliary ganglion lies at least 4.5 cm from the inferior orbital rim. Duke-Elder<sup>9</sup> placed the ganglion just inside the zonule of Zinn, on the lateral side of the optic nerve. This is where

<sup>9</sup> Duke-Elder, W. S. *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 1, p. 195

I found it, from 4.5 to 5 cm back from the inferior orbital margin. Third, in the ophthalmic and anatomic literature there exists considerable confusion and lack of detail as to where and how the motor and sensory nerves enter the orbit<sup>10</sup>

In the cadavers I dissected the pattern was constant. The fourth nerve, to the superior oblique muscle, is definitely outside the muscle cone. It runs along the upper edge of the ophthalmic branch of the trigeminal nerve and enters the superior orbital fissure, together with the frontal branch of the fifth cranial nerve, under the periosteum. It can be blocked only accidentally from an injection inside the muscle cone. The third cranial nerve usually divides into its upper and lower

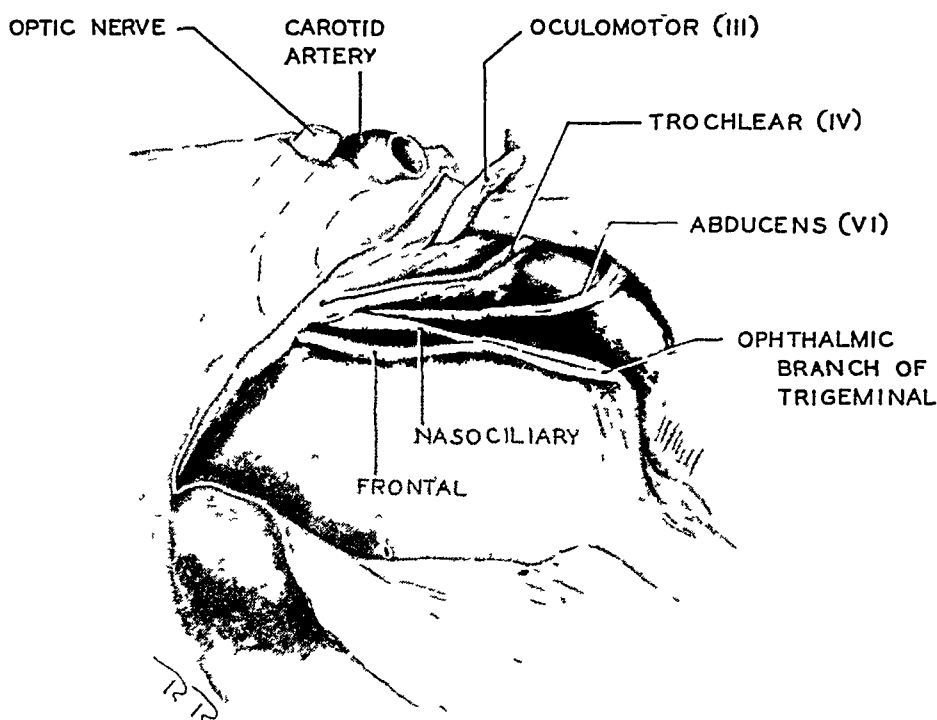


Fig 2—The lateral wall of the cavernous sinus has been reflected, showing the nerves as they enter the left superior orbital (sphenoidal) fissure

branches well back in the cavernous sinus, opposite the ascending curve of the carotid artery. The upper branch enters the superior orbital (sphenoidal) fissure through the lateral edge of the tendon of the superior rectus and levator muscles. It curves on top of the optic nerve and enters the muscle just inside the zonule. The lower branch is much larger. It enters the orbit through the superior orbital fissure just lateral to the optic nerve by curving over the tendinous upper edge of the lateral

<sup>10</sup> Duke-Elder,<sup>9</sup> p 189. Kronfeld, P. C. *The Human Eye in Anatomical Transparencies*, Chicago, Bausch & Lomb Company, 1943, p 62. Rea, R. L. *Neuro-Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, pp 39-41. Walsh, F. B. *Clinical Neuro-Ophthalmology*, Baltimore, Williams & Wilkins Company, 1947, pp 95-127.



rectus muscle Two distinct heads to this muscle were not observed The upper edge forms a horizontal tendinous band, over which the lower branch of the third cranial nerve passes This branch curves under the optic nerve and divides immediately into the branch to the medial rectus muscle and the branch to the inferior rectus and inferior oblique muscles The motor root to the ciliary ganglion is short and is given off just after the branch to the medial rectus muscle The ciliary ganglion lies on the lower branch of the third cranial nerve, just lateral to, and slightly below, the optic nerve The sixth cranial nerve lies just below, and slightly lateral to, the lower branch of the third cranial nerve as it curves over the tendon of the external rectus

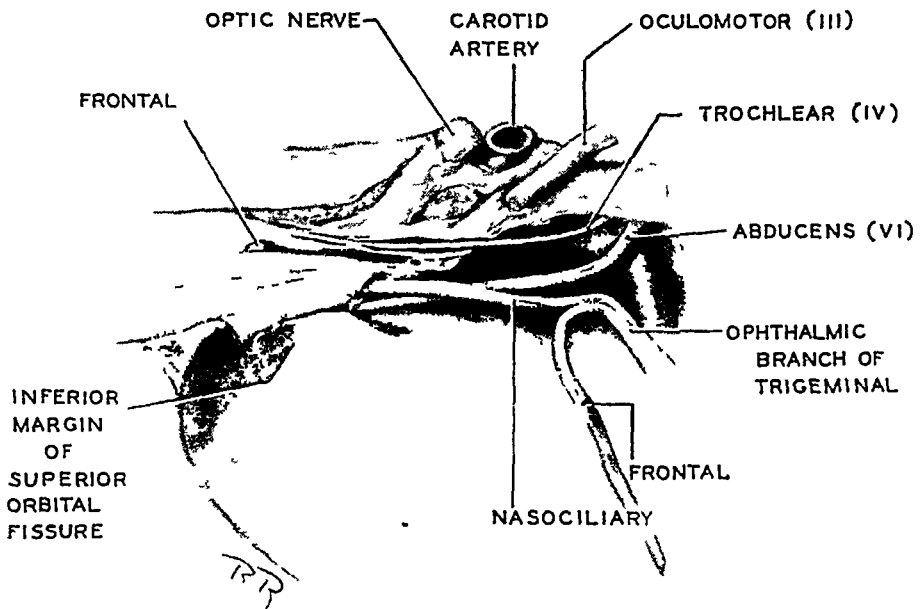


Fig 3—The bone over the optic canal, the superior orbital (sphenoidal) fissure and the roof of the orbit have been removed, showing the nerves as they enter the periosteum of the orbit

muscle It runs along the inner surface of the muscle for 1.5 to 2 cm before entering the latter The nasociliary branch of the fifth cranial nerve is the farthest lateral It enters the orbit just lateral to the lower branch of the third nerve, passing over the tendon of the external rectus muscle This tendon is a constant landmark The sixth cranial nerve, the nasociliary nerve and the lower branch of the third cranial nerve were always found close together as they passed over this tendon to enter the orbit This region, therefore, is the ideal place at which to block these nerves The upper branch of the third nerve was considerably higher, about 3 mm, and ran along the top of the optic nerve In order to block this branch from inside the muscle cone, one must place the needle slightly higher If this region of the orbit is to be reached, a needle at least 5 cm in length must be used

In order to determine what happened to the solution when it was injected this far posteriorly, injections of methylene blue were made in 3 stillborn fetuses. In these fetuses there was no circulation of blood, and the dissection was made several hours after the injection. The dye was observed to be fairly well retained inside the muscle cone and to have come forward, staining the sclera as far forward as the insertions of the rectus muscles. The dye was not found posterior to the sphenoidal fissure, but the optic nerve in the orbit was stained completely in two injections.

In 1 case studied post mortem, 70 per cent iodopyracet U S P ("diodrast") was injected shortly after death, and roentgenograms were

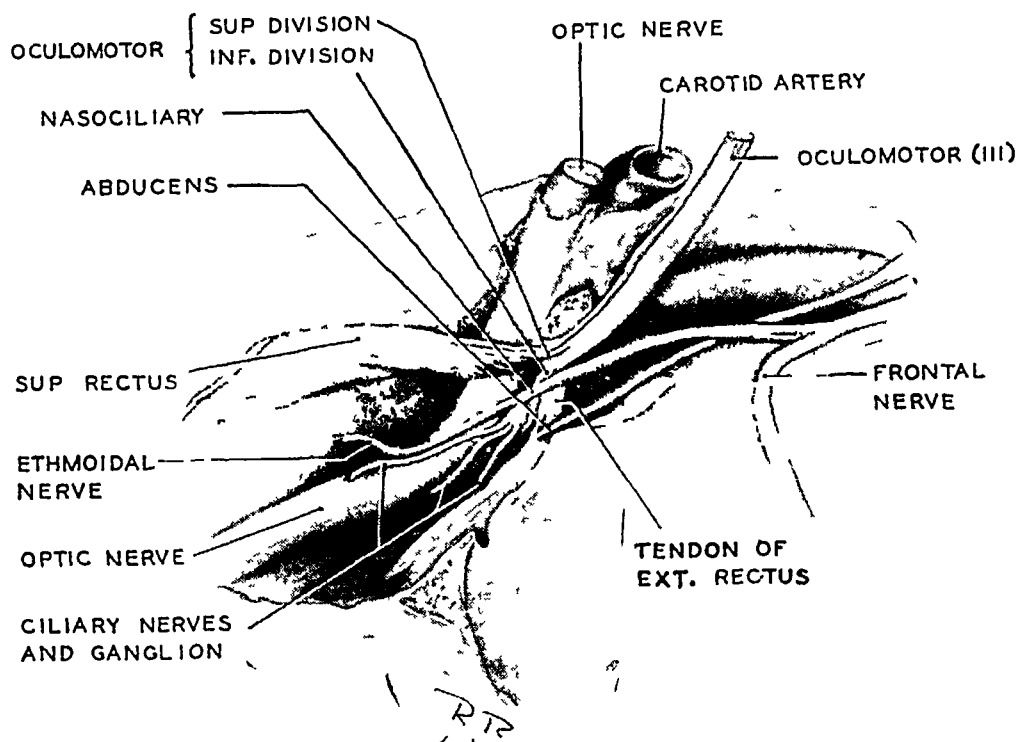


Fig 4—The periosteum of the orbit has been removed and the zonular ligament split just lateral to the tendon of the levator and superior rectus muscles. These muscles are cut anteriorly and turned back, showing the lower branch of the third cranial nerve, the sixth nerve and the nasociliary branch of the trigeminal nerve as they cross over the upper edge of the tendon of the external rectus muscle.

taken of the skull (fig 5). The material was found to come well forward behind the globe. It was retained in the muscle cone, some of the material possibly going back into the middle fossa.

It was difficult to set up a standard for the percentage of effectiveness of the anesthesia. This was estimated only roughly, depending on the patient's reaction when the lids were picked up. The conjunctiva at a distance from the limbus was not affected by blocking the nasociliary nerve, it had, therefore, to be anesthetized with local instillation or infiltration.

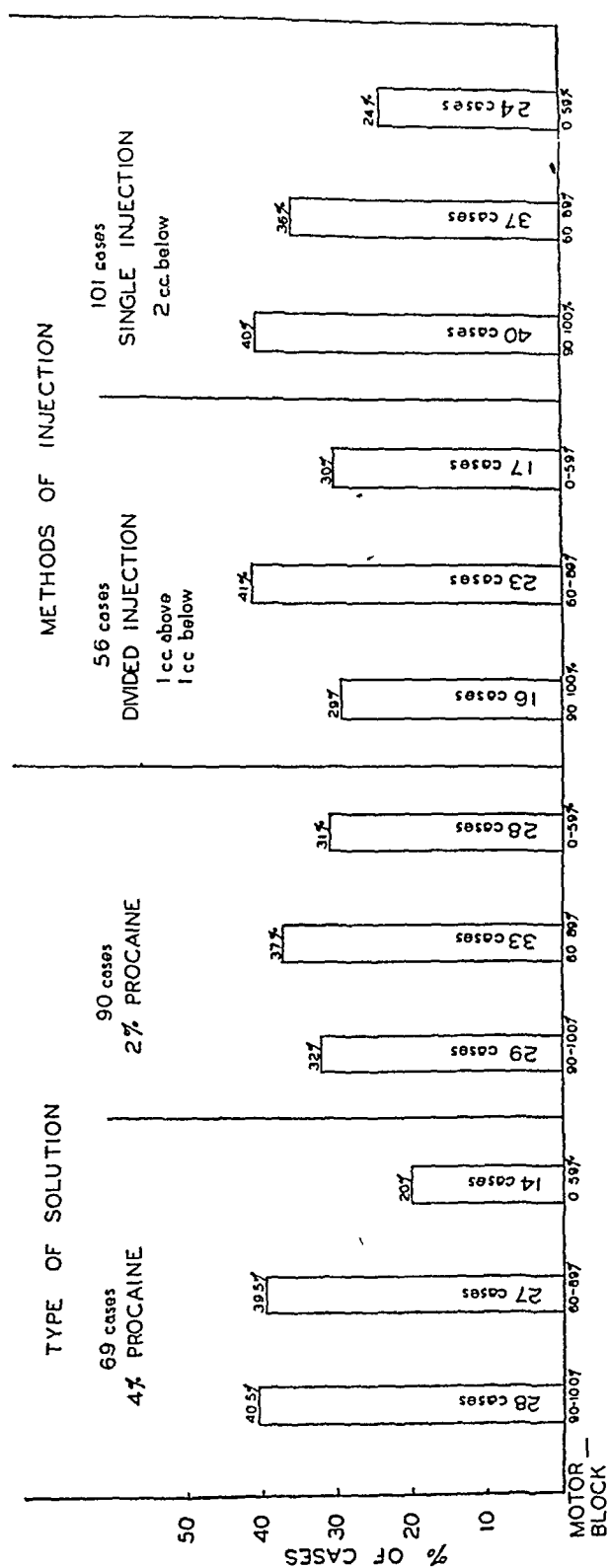


Fig 7—Relation of strength of solution of procaine hydrochloride and method of injection on the motor block

inserted through the skin just inside the lower temporal rim of the orbit. It is then directed toward the apex of the orbit so that it will go through Tenon's capsule midway between the lower edge of the external rectus and the lateral edge of the inferior rectus muscle. Tenon's capsule can usually be felt, and if the patient has the eye rotated upward, the pressure of the needle passing through the fascia will pull the eye down. A quick, short thrust when this is seen or resistance is felt places the needle inside the muscle cone. From here the needle is simply "floated" back, with the aim the upper lateral corner of the orbit. If any obstruction is felt, the direction is changed slightly,

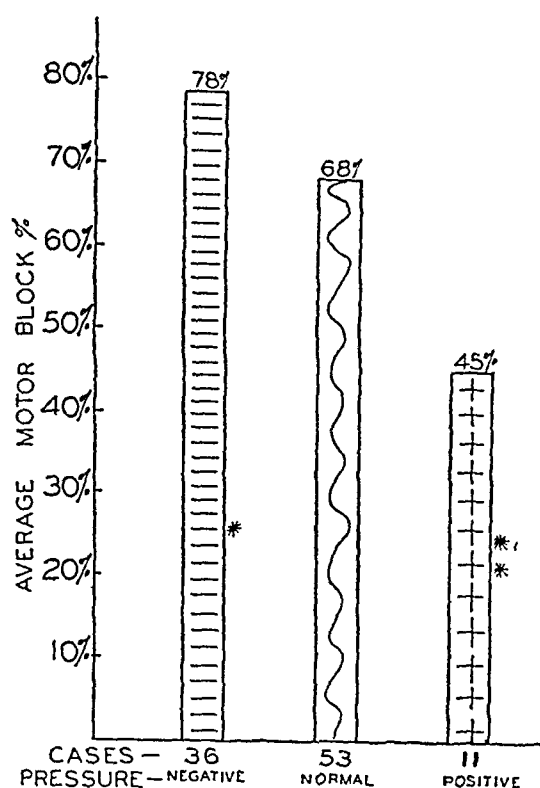


Fig 8—Relation of motor block to vitreous pressure in 100 cases. The asterisk indicates loss of vitreous.

either downward or more medially, until the needle can again be advanced. No force is used at any time after Tenon's capsule has been passed. The tip of the needle is kept lateral and high, following the lateral wall or the roof of the orbit until the full 5 cm is reached. This procedure is like sliding a pencil into the apex of a funnel. When the orbital walls or the under surface of the muscle is touched, the patient may feel a deep, sharp pain. When the deepest point has been reached, 0.5 cc is injected. With the needle still in place, the patient is now asked to move the eyes up and down, right and left, and the movements of the eye and lid are observed. If there is a slight ptosis, or if the eye does not move upward as well as the other eye, one can be quite sure that the superior branch of the oculomotor

nerve has been blocked. If, after a minute or two the superior rectus muscle is still functioning, the second 0.5 cc of the solution is injected in the same place. The needle is now withdrawn slightly, 3 to 5 mm, the tip lowered about 4 mm and the needle again pushed gently back to the full 5 cm. This should put the tip of the needle just below the optic nerve, in the region of the lower branch of the oculomotor nerve, the nasociliary branch and the sixth nerve. The second 1 cc can now be injected, with a good chance of blocking all three of these nerves. The last cubic centimeter may be divided into two parts, the last 0.5 cc being placed slightly lower still, or slightly more lateral if the lateral rectus muscle is still functioning.

I have called this method the "floating" technic, since at no time is any force used. The plunger of the syringe should be withdrawn slightly before injection each time that the position of the needle tip has been changed. If the needle cannot be floated in the full 5 cm, it should not be forced. The one venous hemorrhage I have had was caused by trying to force the needle in too deep. I could feel it perforate something, most probably the inferior orbital vein. My partner had one orbital hemorrhage, and I have had a second one recently.

There is, undoubtedly, slightly more chance of producing hemorrhage in the orbit with this deep multiple injection, but such a complication means merely postponing the operation. A massive loss of vitreous usually means the loss of the eye. I have not seen a massive loss of vitreous since using this deep orbital technic, in spite of the fact that the motor block was good in only 75 per cent of the cases. A poor motor block and a strong protective reflex have not yet come together in the same patient.

The optic nerve could be injured with a 5 cm needle, as pointed out by Lowenstein<sup>12</sup> and Duverger<sup>13</sup>. I have not seen any clinical evidence of such injury in my cases. Vision and visual fields for finger motion were always as good as the state of the eye permitted. The nerve sheath appears to protect the optic nerve from the procaine, bathing it. Enough force actually to puncture the nerve is never used.

No local toxic effect in the orbit was seen when 2 per cent procaine hydrochloride was used. With either intracaine hydrochloride ( $\beta$ -diethylaminoethyl-p-ethoxybenzoate hydrochloride) or 4 per cent procaine hydrochloride, I observed some orbital reaction in a few cases. Occasionally there is slight immediate engorgement of the conjunctival vessels. This may be due to pressure on the venous channels in the posterior orbit. I am not sure about this, since it was seen only a

12 Lowenstein, A. Ueber regionale Anesthesia in der Orbita, *Klin Monatsbl f Augenh* 46: 592-607, 1908.

13 Duverger, C. L'anesthesia locale en ophthalmologie, Paris, Masson & Cie, 1920.

few times and caused no trouble during the operation. In a patient given an injection preparatory to operation for acute glaucoma, there developed generalized tremors with rapid pulse and respiration, lasting about three minutes. In this case the procaine may have been injected into a venous sinus.

The advantage of being able to operate on an eye which cannot be moved by the patient and which is insensitive to pain is so great that these possible dangers are overshadowed. In cataract surgery, the reduction in the vitreous pressure reduces the loss of vitreous to a minimum. The lowering of intraocular tension has been pointed out as an objectionable feature of retrobulbar anesthesia when used in cataract surgery. Atkinson<sup>14</sup> and others expressed the belief that this softening of the globe makes the extraction more difficult. In my opinion this feature is highly desirable. If the eye is soft, the surgeon can always increase the posterior segment pressure merely by using more pressure. He can control this pressure. If, however, the vitreous pressure is positive, the surgeon is at the mercy of the patient, who is in no position to do anything about it. In glaucoma surgery, the lowered tension at the time of the operation is certainly a factor of safety worth having. This type of anesthesia and motor block makes painless enucleation of even the most inflamed eye. The muscles may be pulled or stretched without pain. The muscles do not retract, making it easier to suture them around an ordinary implant or one of the Cutler type. For the same reason, operations for strabismus may be done without pain. A better estimation of the amount of fibrosis is possible when the muscle is completely relaxed. In operations for retinal detachment, relaxation of the muscles makes it much easier to work around and under them. It is seldom necessary to detach a muscle, and the operation is really painless. The blocking of any afferent pain stimulus or axon reflex, is, I believe, an important factor in producing less postoperative reaction.

#### CONCLUSIONS

An attempt has been made to extend the usefulness of retrobulbar anesthesia by producing a motor block of the extraocular muscles. The use of a 5 cm needle "floated" into the apex of the orbit from below and laterally has not proved dangerous. I have experienced orbital hemorrhage in only 2 cases, and this caused no damage to the eye.

Using 2 cc of 2 or 4 per cent procaine hydrochloride, with 0.4 cc of epinephrine hydrochloride to the ounce (29 cc)\*, I was able to produce a better than 60 per cent motor block in 74 per cent of 158 cases.

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<sup>14</sup> Atkinson, W. S. Local Anesthesia in Ophthalmology, *Arch Ophth* 30:777-808 (Dec) 1943.

The posterior segment, or vitreous, pressure was found to be considerably lower when this motor block was good

Of 100 cases of intracapsular cataract extraction, vitreous was lost in only 1, in which the motor block was good, and in 2 others, in which the motor block was 20 per cent or less, a percentage loss of 3

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### ABSTRACT OF DISCUSSION

DR GARRETT L SULLIVAN, Boston In my experience with military and civilian surgery, I have found two factors of importance in achieving effective local anesthesia and akinesia The first is adequate pre-operative medication A calm, relaxed patient may spell the difference between success and failure, especially in cataract surgery

The second important consideration is that the surgeon be patient and allow time for full effect of the anesthetic to develop The first sensation of pain is sufficient stimulus to set the patient in a state of apprehensive anticipation of more to come The surgeon who can bide his time for at least ten minutes after injection will usually be rewarded with more efficient anesthesia and akinesia

As measured by Dr Gifford's standard, I have observed 90 per cent motor block following the retrobulbar injection of 1 cc of 4 per cent procaine hydrochloride, using a 3.5 cm needle This suggests that as good an effect can be obtained with a needle 1.5 cm shorter than that recommended by Dr Gifford I should like to ask whether he can tell us what happens to the solution of the retrobulbar injection within the muscle cone when a 3.5 cm needle is used? Is it not reasonable to assume that, given time, the procaine will find its way to the apex of the muscle cone? His percentage effectiveness of motor block following deep orbital injection is good I suggest that a comparative study be made of his results and those of retrobulbar injection when a 3.5 cm needle is used

The danger of orbital hemorrhage with deep orbital injection seems to be greater, since the point of the needle would be in an area where vessels are larger and more fixed in position The possibility of injecting the local anesthetic into the circulating blood would, likewise, be greater I have seen orbital hemorrhages result from retrobulbar injection in 2 cases, like Dr Gifford, I found that they caused simply postponement of the operation The "floating" technic described by Dr Gifford has apparently been safe in his hands He has stated that there is little, if any, danger of penetrating the sheath of the optic nerve Has he tried to inject the optic nerve of cadavers? One wonders how much pressure is required to penetrate the sheath of the optic nerve

Because of the possibility of retrobulbar hemorrhage, some surgeons elect to inject procaine under the four rectus muscles There is undoubted merit in this procedure, theoretically, it should yield an 80 per cent motor block, as well as effective anesthesia

As pointed out by Dr Gifford, the tonicity of the extraocular muscles plays a significant role in loss of vitreous, and his statistics demonstrate that the more effective the motor block, the lower the incidence of this complication However, it should be emphasized that the tonus of the extraocular muscles is by no means the sole cause of

loss of vitreous Inadvertent pressure on the speculum by the surgeon or his assistant may cause rupture of the hyaloid membrane and resultant escape of vitreous More commonly, inadequate akinesia of the orbicularis oculi provides an opportunity for the patient to squeeze his lids, pressing the speculum on the globe and ultimately causing rupture of the hyaloid membrane

Dr Gifford has proposed a concept of vitreous pressure, suggesting as a factor an inherent pressure within the vitreous body Such a concept may be applied to certain types of glaucoma in which there is an actual increase in the volume of the vitreous In non-glaucomatous cataractous eyes, however, it seems that the cause of escape of vitreous from the eye always lies in pressure on the scleral covering It may be that basically his concept is consistent with this idea, if this is so, the term vitreous pressure may not be most appropriate

At the Massachusetts Eye and Ear Infirmary, 4 per cent procaine hydrochloride has been used for several years in all operations on the eye The chief value of this strong solution probably lies in the fact that more rapid anesthesia and akinesia can be obtained with a smaller amount of the anesthetic The 2 per cent solution would undoubtedly be equally as effective if sufficient time were allowed for it to act Although it is generally recognized that systemic toxicity may result from the use of procaine, I know of no occurrence during these years of either local or general toxicity, and I question Dr Gifford's reference to the local toxic effects of the 4 per cent solution It is quite likely that pressure caused the venous engorgement observed

Some surgeons believe that the lowered intraocular pressure resulting from retrobulbar anesthesia is undesirable, especially in cataract operations I agree with Dr Gifford that the advantages of lowered pressure outweigh the objectionable features Extraction of the cataract may take somewhat longer, but patience and perseverance will usually result in an uncomplicated removal of the lens I cannot, however, agree with his statement that the surgeon is able to control the pressure at will Such a statement presupposes knowledge of how much pressure the hyaloid membrane will tolerate Obviously, the surgeon can exert only that amount of pressure which his own judgment and experience dictate to be safe The result in the individual case will prove his judgment to have been correct or incorrect

DR EDWARD BURCH, St Paul Despite the objection of a few ophthalmic surgeons to the employment of retrobulbar injection of local anesthetic agents, principally procaine, it is clearly the consensus that such a procedure as a routine preoperative measure constitutes one of the most worth while advances in local anesthesia of the eye in recent years This is believed to be particularly true with respect to the extraction of cataractous lenses, the surgical relief of increased intraocular tension and the repair of retinal detachments

Any innovation or new technic in the injection of local anesthetics into the muscle cone therefore deserves careful consideration The widespread acceptance of any new method, such as the one which Dr Gifford has outlined, will largely depend on four factors (1) whether it is a safe procedure, (2) whether it is effective, (3) whether it can be executed without undue difficulty and (4) whether it confers distinct advantages over procedures now in vogue



What elements of hazard may be recognized in deep orbital injection? The danger of introducing pathogenic bacteria into the orbit, of course, must be mentioned, but if the principles of asepsis are observed the risk on this score is remote. Furthermore, if infection should become established, highly potent chemotherapeutic and antibiotic agents are readily available. The danger of infection cannot, therefore, be regarded as a serious objection. Of greater significance is the possibility of inflicting damage with the needle on important structures, particularly the optic nerve and the blood vessels behind the eye. Although the orbital segment of the optic nerve is invested with a tough dural covering, it is theoretically possible, as Dr Gifford has shown in his anatomic studies, for the 5 cm needle to impinge on the nerve. Unquestionably, penetration of the nerve sheath would result in a grave complication, which cannot be lightly disregarded. Hemorrhage behind the eye is another risk which accompanies any deep orbital injection. In Dr Gifford's series, 1 case of such a hemorrhage was encountered, while it occurred in another case during an injection performed by his associate. During the past fifteen years I have seen but 2 retrobulbar hemorrhages when Atkinson's technic of injection of the muscle cone with a 3.5 cm needle was employed. Hemorrhage following orbital injection is not ordinarily a serious matter and requires merely the postponement of operation for a few days. The possibility that the tip of the needle will break off because of a violent movement of the patient comes to mind. If new stainless steel needles of good quality are used, the patient has received adequate preoperative sedation and the use of force in introducing the needle is sedulously avoided, as Dr Gifford has counseled, the danger of this complication is remote.

In addition to the hazards involved, one should consider the reaction of the patient to the pain and discomfort entailed by the injection. If the needle is introduced into the orbit through a previously prepared intradermal wheal, no appreciable pain is experienced by the patient as the needle pierces the skin. It is my impression, however, that, once the needle traverses the orbital fascia and penetrates deep into the orbit, greater pain is elicited with a long, 5 cm, needle than when the conventional muscle cone injection with the shorter, 3.5 cm, needle is used. At least such has been the case in my admittedly brief experience. Perhaps with greater practice, it will be possible to effect the deep injection with less discomfort to the patient.

Dr Gifford's data are ample evidence that his technic will produce motor block and decreased posterior segment pressure in a satisfactorily high percentage of cases. In the few cases in which I have employed Dr Gifford's technic I have found that the eye was in excellent position for operation after the injection and that the decrease in vitreous pressure was gratifying. It might be of interest to undertake a comparative study of the results of Dr Gifford's technic and those of conventional muscle cone injection, employing the criterion for muscle block which he suggested. I should like to inquire whether Dr Gifford has made any such comparison of the two procedures.

With regard to the negative pressure which follows section of the globe when retrobulbar injections have been made, one point deserves comment. Occasionally, if the negative pressure is pronounced, and an attempt at intracapsular extraction is unsuccessful, owing to rupture of the capsule, some difficulty in expressing the lens may be encountered.

I wonder whether Dr Gifford would be willing to express an opinion as to whether the hypotony produced by his technic is more profound than that with the conventional injection, especially if greater amounts of procaine-epinephrine solution are used. Ophthalmic surgeons who perform the extracapsular operation routinely might find the more extreme degrees of decreased pressure a source of embarrassment if this is the case.

I am of the opinion that if the operator possesses a sound knowledge of the anatomy of the orbit and is accustomed to making retrobulbar injections, no undue difficulty will be experienced and the technic can be successfully mastered.

Dr Gifford's method of deep orbital injection involves slightly greater risk than the orthodox injection of the muscle cone, but, on the basis of the evidence he has presented, produces a more effective motor block and results in a higher incidence of normal or negative vitreous pressure than does the older technic. It probably entails somewhat greater discomfort to the patient in its execution and is slightly more difficult to carry out properly. Its greater effectiveness, however, particularly in cataract surgery, is distinctly a point in its favor.

DR PURMAN DORMAN, Seattle. Owing to rules of the Section regulating the time allowed for presentations, Dr Gifford was unable to include in his paper some of his points for later discussion or to give his motion picture. I should like to have my own discussion time devoted to the presentation of the motion picture.

DR EVERETT L. GOAR, Houston, Texas. No one has mentioned the fact that if a retrobulbar injection is properly made orbital hemorrhage will not occur. It is necessary continuously to inject the solution ahead of the needle tip as it passes through orbital tissue. I have made hundreds of such injections and since adopting that method have never had a hemorrhage. However, I have never used a needle longer than 3.5 cm.

DR HAROLD GIFFORD JR, Omaha. I have presented this paper with misgivings, for I know that this procedure is a little more dangerous than the older ones. Undoubtedly, there is more danger of orbital hemorrhage with the longer needle, however, I had used a 3.5 cm needle for years and could never get much, if any, motor paralysis. With the 5 cm needle we have been trying to produce akinesia and anesthesia and avoid loss of vitreous. We are getting closer to our goal, we are not there yet, but I know that we have prevented loss of vitreous in many cases. In fact, only 3 cases in 100 is not a bad showing.

(A short motion picture was shown to demonstrate the technic of deep orbital injection.)

The reasons for failure are twofold. Some orbits are too long, one cannot get back far enough. In persons with fat faces and fatty tissue in the orbits, the procaine does not have the effect that it has in thin people. I am sure the reason has something to do with the consistency of the fat in the orbit. I believe that if the surgeon will use this method he will be much happier in doing cataract extractions. It gives one a wonderful feeling of relaxation to know that the eye will stay where it is and that vitreous is not going to be squeezed out.

# RESPONSES TO THE ISHIHARA TEST FOR COLOR PERCEPTION

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AND

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SEVERAL tests have been devised to detect abnormalities of color perception. The easiest, and the most convenient for mass examination, are those using the pseudoisochromatic plates, of which the Ishihara test is one. Owing to the ease with which it can be made, this test has been used frequently to determine the incidence of defective color vision in various groups of people. We are not aware of any such study having been made among Filipinos.

## METHOD AND MATERIAL

This study was conducted on students seeking admission to the University of the Philippines. In order to avoid their faking results, it was made clear that the results of the test would have nothing to do with their admission to the university. The 16 plate edition of the Ishihara test book, printed in Tokyo, Japan, in 1932, was used. The plates were numbered consecutively from 1 to 13 (the last 3 plates, for illiterates, were not used) and were placed about 60 inches (150 cm) from the subject in an open hall with indirect sunlight. The subject was asked to write down the digit he saw in each plate with his two eyes. Those who hesitated, who read with difficulty or who misread or otherwise saw digits other than those supposed to be seen by persons with normal color perception were retested at a distance of 30 inches (90 cm). The subjects reexamined were often asked to trace the figures they claimed to have seen. A response other than that stated for normal persons in the key for each plate was considered an error or a miss.

## RESULTS

A total of 959 male and 977 female subjects were tested. The distribution of the subjects according to total errors scored and the plates on which the errors were made are shown in tables 1 and 2. Of the male subjects, 43.2 per cent made perfect scores, that is, without a single miss. An equally large number made 2 mistakes, mostly on plates 10 and 11. It was surprising how large was this group of subjects who saw, though with difficulty, the hidden figures in these plates alone without failing on the other plates. The hidden digits are visible

to normal persons<sup>1</sup> more frequently under daylight than under tungsten illumination<sup>2</sup> Deuteranopic and deuteranomalous subjects are less likely to see the hidden figures under tungsten light than under average daylight Our illumination probably had a color temperature between that of average daylight and that of tungsten light We wonder whether the type of illumination we used, fading of the plates or persistence of the subjects in looking for the hidden figures was partly responsible for the large number of subjects discerning the digits It is interesting to note, however, that all subjects who scored 2 errors or more saw

TABLE 1—*Distribution of Male Subjects According to Errors Made*

(a)	(b)	(c)	Male Subjects Who Misread (Expressed in Percentages of Column b)												
Errors Scored by Each Sub ject	No of Sub jects	Total No of Male Subjects (%)	Plate 2	Plate 3	Plate 4	Plate 5	Plate 6	Plate 7	Plate 8	Plate 9	Plate 10	Plate 11	Plate 12	Plate 13	
0	415	43.2													
1	47	4.9	2		2	4					55	36			
2	450	46.9				1					99	99			
3	6	0.6				50				17	33	100	100		
4	1	0.1								100	100	100	100		
6	2	0.2	50	50	100					100	50	100	100	50	
7	1	0.1			100		100	100	100	100	100	100	100		
8	3	0.3	67		33	100		100	100	100	100	67	67	67	
9	2	0.2		50	100	100	100	100	100	100	100	100	50		
10	2	0.2			100	100	100	100	100	100	100	100	100	100	
11	5	0.5	100	60	100	100	100	80	100	100	100	100	100	60	
12	25	2.6	100	100	100	100	100	100	100	100	100	100	100	100	
Total	959	99.8													
Male subjects who misread each plate (expressed in percentage of total no of male subjects who made mistakes)			6.3	5.5	7.2	8.7	6.4	6.8	7.7	7.7	95.7	93.7	6.6	5.9	
Male subjects who misread each plate (expressed in percentage of total no of male subjects)			3.5	3.0	4.1	4.8	3.7	3.9	4.4	4.4	54.3	53.2	3.8	3.3	

the hidden digits in either or both plates Judging from the percentage of the subjects who failed on plates 10 and 11, it would seem that these plates might give misleading values regarding the incidence of persons with defective color vision We are in agreement with the statement of Hardy, Rand and Rittler<sup>3</sup> that this series of plates is the

1 Collins, M Tests in Common Use for the Diagnosis of Colour Defect, Nature, London 140 569, 1937

2 Hardy, L H, Rand, G, and Rittler, M C Effect of Quality of Illumination on Results of the Ishihara Test, Arch Ophth 36 685 (Dec) 1946

3 Hardy, L H, Rand, G, and Rittler, M C Tests for Detection and Analysis of Color Blindness II Comparison of Editions of the Ishihara Test, Arch Ophth 35:109 (Feb) 1946

least satisfactory in the Ishihara test because a considerable number of persons having normal color vision see the hidden digit, thus failing the plate

Disregarding, therefore, the results in plates 10 and 11 and using Miles's criterion<sup>4</sup> for designating a subject as having defective color vision (that is, a subject has defective color vision when he makes 2 or more out of a possible 10 errors), we obtain 4.3 per cent as our incidence of defective color vision. On the basis of Hardy, Rand and Rittler's observations that no subject with low normal color vision scores less than 75 per cent,<sup>5</sup> or makes 4 or more errors out of a possible 12, we computed and obtained the same incidence of defective color vision,

TABLE 2—*Distribution of Female Subjects According to Errors Made*

(a) Errors Scored by Each Sub- ject	(b) No of Sub- jects	(c) (b) × 100 Total No of Female Subjects (%)	Female Subjects Who Misread (Expressed in Percentages of Column b)											
			Plate 2	Plate 3	Plate 4	Plate 5	Plate 6	Plate 7	Plate 8	Plate 9	Plate 10	Plate 11	Plate 12	Plate 13
0	540	55.3												
1	81	8.2				8.6					69.1	21.0	1.2	
2	351	36.0				1.1				0.3	99.7	98.8		
3	3	0.3				100.0					100.0	100.0		
7	1	0.1	100.0		100.0	100.0			100.0	100.0	100.0	100.0		
12	1	0.1	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Total	977	100.0												
Female subjects who misread each plate (expressed in percent age of total no. of females who made mistakes)			0.5	0.2	0.5	3.4	0.2	0.2	0.5	0.7	94.0	84.4	0.5	0.2
Female subjects who misread each plate (expressed in percent age of total no. of female subjects)			0.2	0.1	0.2	1.6	0.1	0.1	0.2	0.3	42.1	37.8	0.2	0.1

namely 4.3 per cent. This is close to the 4.1 per cent of male subjects who failed in plate 4, the plate considered by the latter group of workers as ideal for screening persons with defective color vision. Inasmuch as the lighting used in the present study probably did not reach the color temperature of average daylight, as advocated for use in this test,<sup>6</sup> some persons with deficient color vision must have escaped detection.

4 Miles, W. One Hundred Cases of Color Blindness Detected with the Ishihara Test, *J Gen Psychol* **2** 535, 1929.

5 Hardy, L. H., Rand, G., and Rittler, M. C. Tests for Detection and Analysis of Color Blindness. I. An Evaluation of the Ishihara Test, *Arch Ophth* **34** 295 (Oct) 1945.

6 Hardy, L. H., Rand, G., and Rittler, M. C. The Ishihara Test as a Means of Detecting and Analyzing Defective Color Vision, *J Gen Psychol* **36** 79, 1947, footnotes 2 and 5.

Consequently, the values cited are probably lower than those which would be obtained if average daylight illumination had been used

Comparing our data with similar studies on other racial groups,<sup>7</sup> we find that the incidence of defective color vision among Filipinos is less than that among unselected white persons or Chinese, but is higher than that among Mexicans, full-blooded Indians and American Negroes

Of the 36 subjects who made mistakes in plates 12 and/or 13, only 17 were "classified" by the "hit and miss" criterion of Hardy, Rand and Rittler. All the 17 read correctly only the first digit of either or both of these plates, missing or not seeing the red-purple digits. Of the 17, 7 were "classified" by plate 12, 1 by plate 13 and 9 by plates 12 and 13. The classification of these subjects as deuteranomalous or deuteranopic must be made with caution, however, in view of the uncertainty about the color temperature of our illumination.

Of female subjects, only 0.3 per cent had defective color vision (by Miles's criterion), or 0.2 per cent by the criterion of Hardy, Rand and Rittler. Plate 4, in table 2, gave an incidence of 0.2 per cent.

#### SUMMARY

Approximately 2,000 male and female subjects were tested with the Ishihara color plates. Tables are presented showing the percentage of subjects failing on each individual plate and grouping them according to the total number of errors made.

The incidence of male subjects with defective color vision as determined by Miles's criterion, or by Hardy, Rand and Rittler's criterion, which was 4.3 per cent, was almost the same as the incidence of subjects who failed in plate 4, which was 4.1 per cent. For female subjects the two criteria gave 0.3 and 0.2 per cent, respectively, while plate 4 gave an incidence of 0.2 per cent.

A large number of subjects saw the hidden digits in plates 10 and 11 without misreading other plates. Many in this group probably have normal color vision.

In view of what has been found regarding the effect of different types of illumination on the results of the Ishihara test, the values reported here are probably lower than those which would be obtained if "average daylight" illumination had been used.

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<sup>7</sup> Clements, F. Comparative Racial Differences in Color Blindness, *Science* **72** 203, 1930. Garth, T. R. Incidence of Color Blindness Among Races, *ibid.* **77** 333, 1933. Shuey, A. Incidence of Color Blindness Among Jewish Males, *ibid.* **84** 228, 1936. Kilborn, L. G., and Beh, Y. T. The Incidence of Color-Blindness Among Chinese, *ibid.* **79** 34, 1934. Crooks, K. B. M. On the Incidence of Color-Blindness Among Negroes, *ibid.* **80** 269, 1934.

## INTERSTITIAL KERATITIS AND VESTIBULOAUDITORY SYMPTOMS FOLLOWING VACCINATION

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THE report by Cogan<sup>1</sup> of the syndrome of nonsyphilitic interstitial keratitis and vestibulocauditory symptoms, in which the matter of etiology was permitted to remain unsolved, has stimulated interest in this subject. Because of the rarity of diagnosis of this syndrome and because of a suggested etiologic factor in the case to be reported, this paper is submitted as an introductory study of postvaccinal encephalitis

### REPORT OF A CASE

A man aged 30, who had served in the armed forces for slightly over four years, had onset of the acute episode of his illness on March 13, 1945, one hour after the noonday meal, which consisted of pork, vegetables, bread, butter, coffee and canned fruit. The initial symptom was nausea, which was followed shortly by retching and then by vomiting of projectile character. After the vomiting had ceased the patient noticed a persistent dull nuchal ache which did not keep him from his work, although it remained unchanged throughout the rest of the afternoon. There was no chill, dizziness or fever at this time. The patient slept well that night, but on his awakening the next morning he was aware of a rather severe dizziness, in which the bed seemed to turn about in circles. The dizziness vanished sufficiently in a few hours so that he was able to report to work at the usual time. Again, after the noonday meal, which he ate sparingly the symptoms of the previous day recurred, together with an oppressive tightness about the neck. The acute dizziness recurred, and the patient returned to his quarters, where he spent a quiet and comfortable night. On the second day there was no recurrence of the headache. On arising on March 15, the patient was still acutely dizzy and somewhat faint. He was admitted via ambulance to the hospital, where, after a mild bout of retching, the only obvious symptom during the first week was persistence of the dizziness which was more pronounced when the patient was erect. At no time was there any abnormality of temperature. His past history indicated that he had had several virus diseases, all of them mild. He had had several mild attacks of herpes labialis. Mumps, measles, scarlet fever and chickenpox had been contracted, all without any serious sequelae. He had never been hospitalized and had never been ill longer than three days. He had been told that he had mild sinusitis, and during the past three months he had had a cold and cough "on and off." No history of sensitivity to plants or to serums was forthcoming, the patient had had many "shots" during his military career, but none had been followed by disturbing symptoms, in fact, he seemed to suffer less local reaction after an injection than any of his companions.

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1 Cogan, D. Syndrome of Nonsyphilitic Interstitial Keratitis and Vestibulocauditory Symptoms, Arch Ophth 33 144 (Feb) 1945

On March 6 the patient received vaccinia virus and was given a stimulating dose of typhoid and paratyphoid vaccine U S P. There was no systemic or local reaction to the vaccination or to the injection of typhoid vaccine, and the incident had been forgotten completely.

On his admission, the results of physical examination were reported to be entirely normal. The temperature was 98 F, the blood pressure 114 systolic and 86 diastolic, and the pulse rate 86 per minute. There were no positive neurologic signs and no physical findings of significance other than the acute vertigo. The urine was normal. A blood count performed on the day of admission showed a leukocytic count of 11,700, of which 72 per cent were polymorphonuclear cells and 28 per cent were reported as "lymphocytes." Several subsequent blood counts were performed, with a variation of 8,000 to 15,000 leukocytes and maintenance of the previous percentages for the differential count. The reactions to routine tests for syphilis, brucellosis and tularemia were reported as negative. No studies of the spinal fluid were made until ten days after the onset of the illness, at which time the following report was obtained: pressure normal, cell count 0, colloidal gold curve 00000, globulin not increased, total protein 22 mg per hundred cubic centimeters, Wassermann reaction negative.

Roentgenograms of both the skull and the chest were reported as showing nothing abnormal. Because of the persistence of the vertigo without associated symptoms, otologic and neuropsychiatric consultation was sought. The neuropsychiatric consultation, held one week after the patient's admission, is recorded in its entirety because it prevents many interesting side lights.

"The neurologic status was normal. There was no nystagmus or ataxia. No abnormal reflexes were elicited. The cranial nerves were normal. The fundi were normal. The history and physical signs did not indicate an expanding intracranial lesion. The patient had been married about four years, no children had been born. He was a lawyer by formal training and had been a member of the bar in his home state for several years. After his induction into the Army, in February 1941, he took basic training and on its completion was assigned by reason of his previous training, to a legal type of work in division headquarters.

"After several months at this type of work, he applied for officers' candidate school, from which he was eliminated after eleven weeks because of 'lack of leadership in combat.' He was given the opportunity of remaining as an enlisted man at the same camp headquarters, where he continued to work in several capacities requiring legal training, and eventually he was given his present rank of warrant officer. On returning from officially granted leave on Feb. 25, 1945, he learned that he had been relieved of his assignment and had been placed on an available list of men expecting orders for duty elsewhere, possibly overseas.

"For the previous three months he had been feeling generally weak, tired and exhausted. He had always been of a passive personality. He maintained a definite feeling of inadequacy because there had been no children in his marriage. His legal ambitions were of a passive type, and he admitted that he never pictured himself as a successful 'trial' lawyer. While at officers' candidate school, he found the physical program difficult to carry through, and on many occasions he was forced to 'fall out.'

"The patient appeared to be a passive, neurasthenic person. In the service he failed to gain a commission because of lack of physical performance and leadership of men in combat type of duty. After this failure he was given a form of work which was technically and psychologically acceptable to him. As a result of his work, he gained a warrant officer's status, which to him was very gratifying.



"While on leave, he was relieved of his command, without previously being informed, and placed on an 'available' list. Consciously, he took this in a normal manner and reacted with, 'Well, a soldier is never put'. Psychologically, however, he felt that it was a serious failure on his part. With this news there was the threat of combat duty and separation from his wife, on whom he depended a great deal emotionally. He reacted to the situation in the only manner of which he was capable, an acute episode of hysteria. His neurasthenic features had existed for many years and manifested themselves early in his military career. The diagnosis was psychoneurosis and neurasthenia."

Otolaryngologic consultations and studies were of indeterminate value. The patient's history revealed that two years earlier he had had an episode of buzzing in his ears following a period of diving. This buzzing had lasted only two days. As far as the patient could tell, the condition had entirely disappeared. One week after the onset of the acute vertigo the patient complained of auditory disturbances of transient character. He described these as of two distinct types. One was of the "cockleshell variety", the other resembled the hum of an "undialed telephone". The otologist reported the results of his audiometric and labyrinthine studies as being unreliable, transitory, indeterminate and contrary to expectation. Three separate cold water tests were performed in the first two weeks, and in each the patient did not respond normally. Cutaneous douching for two minutes failed to bring on any of the normal signs of an active labyrinth, such as nystagmus, nausea, vomiting, vertigo or past pointing.

From the appearance of the audiogram, the deafness was regarded as a mixed, rather than a plain, type of nerve deafness.

During the patient's first week of hospitalization the only symptom from which he suffered was vertigo. This dizziness appeared to be improving at the end of two weeks. During the second week the transient auditory symptoms appeared. Ocular manifestations made their initial appearance about the first of April, being mild at the onset. The right eye was first involved. There was no pain or secretion. There were mild conjunctival injection and a slight sensitivity to light. After the instillation of a mild astringent (zinc sulfate, 0.25 per cent), the eye appeared to improve and remained comfortable for about ten days, at which time there was a recurrence of similar, but severer, symptoms. Examination at this time disclosed a very mild aqueous flare, increased thickening of the cornea, with several folds in Descemet's membrane, and many "craters" in the zone of specular reflection. Several small foci of increased corneal opacification were located in the stroma. At various places the limbal vessels were beginning to push into the corneal substance superficially. Under treatment with local instillation of atropine and intravenous administration of typhoid vaccine (a series of seven injections was given), the right eye gradually cleared within three weeks, but by this time a similar condition was developing in the left eye. Attacks continued to shift from one eye to the other, each lasting about one week and each clearing completely and leaving no sequela. The attacks appeared unrelated to any other systemic manifestation. During one phase, sulfathiazole was used systemically, without any apparent benefit other than to indicate that the patient was sensitive to that drug, in a subsequent interval penicillin therapy was instituted, with as unencouraging a response. Throughout the course of the ophthalmic illness, partly because of familiarity with the events leading up to the patient's hospitalization, together with the neuropsychiatric diagnosis and the presence of conjunctival secretion even when definite keratitis existed, it was difficult not to suspect malingering.

## COMMENT

In 1904 Aldrich<sup>2</sup> stated

The variolus process possesses, in marked degree, the power to awaken latent predispositions to nervous disease, as well as to independently disorder function and create anatomical alterations in the various nervous structures of the body

In order to explain this rare syndrome of involvement of the vestibuloauditory nerve associated with interstitial keratitis as a form of postvaccinal encephalitis, it is necessary to mention some clinical and much experimental evidence completely outside the scope and purpose of this paper. Some of the recently accumulated literature, however, serves to illustrate by analogy the mechanism which may have been at work in the production of this syndrome. The concatenation of events necessary to explain the entire picture, admittedly, is forged in weakness, there is no lack of realization of this fact. However, the clear-cut nature, rather than the rarity, of the syndrome offers some compensation.

Cogan<sup>1</sup> reported 4 cases of interstitial keratitis associated with vestibuloauditory symptoms. In many respects, the present case simulates those reported by Cogan. In Cogan's cases the cause was unknown and the disease had not run its full course at the time of the report. The transient and evanescent nature of the interstitial keratitis was stressed, but it was impossible to attach etiologic significance to any of the characteristics of the syndrome, although I must confess that when I first read the case reports I felt that there lurked an elusive and little understood virus as an etiologic possibility. Involvement of both divisions of the eighth nerve, together with a portion of the fifth nerve, and an acute cephalgic onset speak for a thoroughly localized cerebral syndrome. Can such a set of circumstances arise after a postvaccinal episode, much as in the postvaccinal encephalitides, with limited and specific localization of cranial nerves, particularly when the cutaneous response to the vaccine is entirely negative? If so, can a response be called forth at the end organs of these cranial nerves in a series of successive waves, gradually tapering off in its severity?

Cogan, in reporting the "syndrome of nonsyphilitic interstitial keratitis associated with vestibuloauditory symptoms," stated that the syndrome had been reported only once previously and the cause was unknown, consequently, the purpose of his reporting these cases was to stimulate further studies. Characteristics of the syndrome is the interstitial keratitis, associated with vertigo, tinnitus and deafness. After a review of Cogan's 4 cases and Mogan and Baumgartner's<sup>3</sup> case and the consideration of the present case, certain clinical features stand out

2 Aldrich, C. I. *Am J M Sc* **127** 198, 1904

3 Mogan, R. F., and Baumgartner, C. I. *West J Surg* **42** 628 1934

rather prominently (1) repeated negative reactions to the Wassermann test and allied serologic studies of the patient, as well as of both parents, (2) bilaterality of both ocular and auditory symptoms, (3) occurrence in young adults, (4) chronicity, with multiple unpredictable recurrences, (5) close time relation between onset of ocular and of aural symptoms, (6) mildness of ocular symptoms, (7) aggravation of symptoms by changes in the weather, (8) striking variation in symptoms, (9) characteristic yellowish white corneal opacities, tending toward vascularization, (10) evidence of iritis, as determined by cells in the anterior chamber and occasional keratic precipitates, (11) leukocytosis and suggestive eosinophilia, (12) bilateral nerve deafness, and (13) constant condition of the cornea

Cogan emphasized the definite difference between the picture of syphilitic interstitial keratitis and that of this syndrome, so that no difficulty in differentiation should be encountered. However, he could draw no conclusion as to the cause of this syndrome. Cogan also noted that during the year in which these 4 cases were observed he encountered only 1 case of active syphilitic interstitial keratitis in his practice. He cited Sagher<sup>4</sup> as authority for the statement that 84 per cent of patients with interstitial keratitis showed a positive serologic reaction or some definite stigma of congenital syphilis. Cogan expressed the opinion that the nonsyphilitic syndrome is commoner than Sagher's percentage incidence would indicate.

Review of the history in each of Cogan's cases did not suggest any etiologic factor similar to that in the present case. However, there were some unusual features in the past history in his cases 1, 3 and 4. In his first case, one of the patient's sisters died at 18 months of age during an influenza epidemic. The patient had a severe cold three months prior to the onset of the syndrome. In case 3 the patient had an attack of "ptomaine poisoning" just prior to the onset of her illness. In case 4 the patient had been exposed to lewisite ( $\beta$ -chlorovinyl dichloroarsine) two years earlier, at which time there were temporary ocular symptoms. In a highly speculative manner, one may assume that case 1 represents a host which is unusually susceptible to certain viruses, whereas case 4 may be an instance of ocular as well as cranioneural pathoclasia, particularly if lewisite may be considered an agent capable of producing acute perivascular myelinoclasia of varying degrees, as shown by Putnam.<sup>5</sup> This speculation is further evidence of the possibilities and ramifications of the original problem.

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4 Sagher, E. *Zentralbl f d ges Ophth* **34** 305, 1935

5 Putnam, T. J. *J Psychiat & Neurol* **44** 460, 1932, *Studies in Multiple Sclerosis "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction*, *Arch. Neurol & Psychiat* **33** 929 (May) 1935, *Disseminated Encephalomyelitis* *ibid.* **41** 1087 (June) 1939, *Bull New York Acad Med* **17** 337, 1941

The case reported by Mogan and Baumgartner<sup>3</sup> as one of "Meniere's disease complicated by interstitial keratitis" is strikingly similar to the present case. The disease began as an iritis and interstitial keratitis in an apparently healthy man aged 26 whose past history and physical examination were without significance. There soon appeared periodic episodes of bilateral involvement, with recurrences every two weeks, each attack lasting three or four days. An explosive type of Meniere's disease occurred two months after the ocular onset. This was characterized by nausea, vomiting, vertigo, tinnitus and deafness. Both ocular and aural attacks were symmetric and regular in frequency. The prodromal symptom indicating an ocular attack was a peculiar conjunctival pallor, followed shortly by hyperemia, corneal cloudiness and pain. Visual acuity was reduced to 20/100 with each attack. The ocular and aural symptoms persisted for four days, with many recurrences during the year, at the end of which time ganglionectomy was performed. There was rapid improvement in and almost complete disappearance of ophthalmic and otologic symptoms.

The authors stated the belief that, because of the striking results obtained with ganglionectomy, a disease of the sympathetic nervous system should be strongly considered as an etiologic factor in Ménière's disease. Histopathologic studies of the resected ganglions revealed chromatolysis and crenulation of the ganglion cells. The significance of these changes was not determined. Foreign protein therapy was administered in this case notwithstanding the fact that a vasomotor storm was suspected, a procedure which apparently is contraindicated (Putnam<sup>5</sup>).

It has been assumed that in the case reported a response to a virus vaccine occurred with the help of foreign protein in the form of typhoid and paratyphoid vaccine, by producing a reaction in sensitized nerve tissue. The possibility that the brain had been sensitized can only be assumed, since the patient was undergoing revaccination. That such an allergic state may be produced in nerve tissue has been shown experimentally, that a very constant incubation period may be shortened, especially when there is no cutaneous "take" has been shown clinically.

The significance of the host in these infections can better be understood by studying a case described by Gentili<sup>6</sup>. This author reported on the occurrence of encephalitis in identical twins, the primary complication in each patient being involvement of the optic nerve. The initial case of encephalitis occurred in twin A at the age of 2 months. The chief complication, bilateral blindness, was the result of optic neuritis. Encephalitis occurred in the second twin at 16 months of age, again, the primary complication was bilateral optic neuritis. In each case there was return of vision to normal after several weeks, yet no clear concept was reached as to the type of encephalitis. The predisposition of these twins to ocular complications particularly with involvement of the visual elements of the brain in a variegated type of

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6 Gentili Lattante 8 286, 1937

encephalitis, not only points toward specificity of neural tissue, but emphasizes the importance of host over virus in the pathogenic picture

Finley<sup>7</sup> conclusively demonstrated that in acute postvaccinal encephalitis the most striking pathologic changes occurred in the perivenous areas. These changes were shown to be an extra-adventitial perivascular reaction with secondary progressive glial proliferation and demyelination along the veins for varying distances. Strikingly, the large, long-coursed vessels showed the most involved perivenous reaction, as reported by Davidoff, Seegal and Seegal<sup>8</sup>. It would seem, therefore, that the distribution of the perivascular lesions is determined in large part by the anatomic relations of the veins of the central nervous system. Finley,<sup>7</sup> in his series of 16 cases with autopsy, demonstrated in all sections of the pons that the large blood vessels were chiefly involved. In the pons the most numerous and the largest veins are branches of the paramedian vein, lying lateral to the median raphe and passing to the basilar vein. Studies of photomicrographs of the pons showed the perivenous glial lesions concentrated about the more medially situated venous channels. The lateral, smaller vessels were hardly involved. Such a distribution could in a measure explain the peculiar bilaterality and the equally peculiar cranial nerve dualism seen in our case. Lucksch<sup>9</sup> noted a perivascular infiltration in the pons in 2 cases with autopsy. Schindelha and Folger,<sup>10</sup> in reporting 4 additional cases of postvaccinal encephalitis (in 1 of which autopsy was performed) found a similar type of reaction in the pons. Greenfield,<sup>11</sup> too, noted the remarkable constancy in the distribution of the lesions in the brain stem and basal ganglions in these cases of encephalitis.

I have tried to show that in the rare syndrome of interstitial keratitis associated with vestibuloauditory symptoms described by Cogan one may be dealing with an atypical encephalitis in which the mode of extension is centrifugal. It is also known that in experimental dendritic keratitis there not infrequently occurs a herpetic encephalitis. It would seem, therefore, that there is some possibility of extension of virus along the fifth nerve in either direction. Such a possibility is not remote in the virus disease of measles, in which the conjunctival and corneal nerve endings are evidently in close relation to the offending virus.

7 Finley, K. H. Perivenous Changes in Acute Encephalitis Associated with Vaccination, Variola and Measles, *Arch Neurol & Psychiat* **37** 505 (March) 1937

8 Davidoff, L. H., Seegal, B. C., and Seegal, D. J. *Exper Med* **55** 163, 1932

9 Lucksch, F. *Med Klinik* **20** 1170, 1924

10 Schindelha and Folger, cited by Glanzmann, E. *Schweiz med Wchnschr* **57** 145, 1927

11 Greenfield, J. G. *Brain* **52** 171, 1929, *J Path & Bact* **33** 453, 1930

## SUMMARY AND CONCLUSIONS

A case of interstitial keratitis associated with vestibuloauditory symptoms is reported and a possible etiologic factor is suggested

In a subsequent communication it is hoped to demonstrate the relation of this syndrome to postvaccinial encephalitis

Stress should be placed on the important role the ophthalmologist should play in the early detection of postvaccinial encephalitis through observation of ocular complications

692 High Street

# RETINOBLASTOMA (RETINAL GLIOMA) CURED BY RADON SEEDS

Report of a Case

JOSEPH WALDMAN, M D

AND

C E G SHANNON, M D

PHILADELPHIA

SINCE the cure or arrest of retinoblastoma by any method of treatment is rare, we believe that any case in which either of these results has been obtained should be reported. It cannot be overemphasized, however, that the method of treatment applied in a single case should not necessarily be used as a rigid criterion for all cases.

Martin and Reese,<sup>1</sup> in an excellent study entitled "Treatment of Retinoblastoma Surgically by Irradiation," listed the cases of spontaneous cure, therapeutic cure and arrest. The same authors<sup>2</sup> have published additional information on their method of roentgenotherapy and the condition of their patients to date. Their results will stand as a monumental contribution to treatment of this malignant disease. Others<sup>3</sup> have reported cases in which treatment with roentgen radi-

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From the Department of Ophthalmology, Jefferson Medical College Hospital Service 2

Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, Oct. 23, 1947

1 Martin, H., and Reese, A. B. Treatment of Retinoblastoma Surgically and by Irradiation, *Arch Ophth* **16** 733-761 (Nov) 1936

2 (a) Martin, H., and Reese, A. B. The Treatment of Retinoblastoma (Retinal Glioma) by a Combination of Surgery and Radiation, *Tr Am Acad Ophth* **45** 70-91 (March-April) 1941, (b) Treatment of Retinoblastoma (Retinal Glioma) Surgically and by Irradiation, *Arch Ophth* **27** 40-72 (Jan) 1942, (c) Treatment of Bilateral Retinoblastoma Progress Report, *ibid* **33** 429-439 (June) 1945 (d) Reese, A. B. Effects of Radiation on the Eye, *Am J Ophth* **29** 1160-1162 (Sept.) 1946

3 Smaltino, M. Glioma Cured by Roentgenotherapy Report of Case, *Boll d'ocul* **15** 551-568 (May) 1936 (b) Ronstrom, H. Glioma Treated with Roentgen Rays Observation Through Period of Twelve Years, *Acta ophth* **14** 361-379, 1936 (c) Bokerman, L. Roentgenotherapy of Glioma Report of Case, *Ztschr f Augenh* **91** 348-352 (April) 1937 (d) Schevling, H. Roentgenotherapy of Glioma, *Klin Monatsbl f Augenh* **98** 756-762 (June)

ation or with radium met with varying degrees of success. Excision of intracranial extensions of glioma has been combined with enucleation.<sup>4</sup> Retinoblastoma has also been treated by direct electrocoagulation, with inconstant results.<sup>5</sup>

One of us (J W) described a new method of applying radon seeds for ocular disorders.<sup>6</sup> This method was devised to overcome the difficulties that may occasionally be encountered in inserting radon seeds directly into the tumor<sup>3</sup> or in applying them, embedded in dental stent, to the overlying sclera of the posterior part of the globe in cases of retinoblastoma, as described by Stallard.<sup>7</sup> Briefly, the method consists in the application of a thin, semipliable chromium-plated or rhodium-plated silver band applicator containing depressions in the distal end into which the required number of radon seeds fit (fig 1)

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1937 (e) Knapp, P. Permanent Cure of Glioma by Roentgen Irradiation, *ibid* **99**:527 (Oct) 1937, further report on Knapp, P, and Ludin, M. Cure of Retinal Glioma by Irradiation, *ibid* **83** 279-284 (Aug-Sept) 1929 (f) Weiterschau, J. Radiation Treatment of the Retinal Glioma, *ibid* **102**:359-372 (March) 1939 (g) Baillart, P, Bellot, A, and Tilli, H. Bilateral Glioma Treated by Radium. Report of Case, *Bull Soc d'opht de Paris* **51**:364-369 (June) 1939 (h) Anderson, J R. Prognosis and Treatment of Retinoblastoma, *Ophthalmologica* **98** 193-200 (Dec) 1939 (i) Jushaus, R. Prognosis of Glioma, *Klin Monatsbl f Augenh* **105**:45-54 (July) 1940 (j) Schoenberg, M J. Case of Bilateral Glioma of Retina, *Arch Ophth* **48**:485, 1919, Case of Bilateral Glioma of Retina, Cured in Non-Enucleated Eye by Radium, *ibid* **56** 221-228 (May) 1927 (k) Sorsby, A, cited by Traquair, H M, in discussion on Hine,<sup>3m</sup> p 105 (l) Moore, R F, Stallard, H B, and Milner, J G. Retinal Gliomata Treated by Radon Seeds, *Brit J Ophth* **15** 673-696 (Dec) 1931 (m) Hine, M L. Diseases of the Retina, *Tr Ophth Soc U Kingdom* **64**:99-106, 1944, (n) *ibid*. **57**:173-186, 1937 (o) Philips, S. Radon Seeds in the Treatment of Glioma Retinae, *ibid* **64**:107-114, 1944 (p) Joyce, A. Glioma of the Retina Cured by Radon Seed Implantation, *Tr Ophth Soc Australia* **4** 98, 1944

4 (a) Jean, G W. Discussion, *Arch Ophth* **51**:505, 1922, cited by Ray and McLean.<sup>4b</sup> (b) Ray, B S, and McLean, J M. Combined Intracranial and Orbital Operation for Retinoblastoma, *Arch Ophth* **30** 437-445 (Oct) 1943 (c) Dott, N. J, and Meighan, J. Intracranial Resection of the Optic Nerve in Glioma Retinae, *Am J Ophth* **16** 59, 1933 (d) Rand, C W. Glioma of the Retina. Report of a Case with Intracranial Extension, *Arch Ophth* **11**:982-994 (June) 1934 (e) Shannon, C E G, Jaeger, R, and Forster, F M. The Combined Intracranial and Orbital Operation for Bilateral Retinoblastoma, *Tr Am Ophth Soc* **62** 326-333, 1944

5 Weve, H J M. Electrocoagulation and Use of Diathermy in Ophthalmology, abstracted, *Am J Ophth* **18**:575 (June) 1935 deRoethth. Treatment of Bilateral Retinoblastoma, *Northwest Med* **43**:364, 1944

6 Waldman, J. A New Method of Applying Radon Seeds for Ocular Disorders, *Arch Ophth* **23**:55-59 (Jan) 1941

7 Stallard, H B. A New Technique for the Application of Radon Seeds to the Sclera in the Treatment of Glioma Retinae, *Brit J Ophth* **22**:604 (Oct) 1938



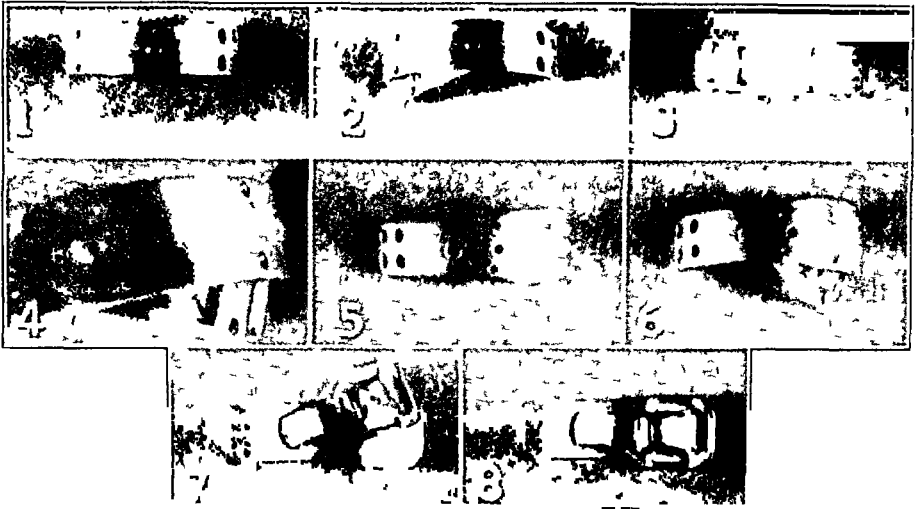


Fig 1—The applicator for two radon seeds is shown in 1 to 4, inclusive, slightly enlarged, the applicator in 4 being enlarged approximately three times, and the applicator for four seeds is shown in 5 to 8

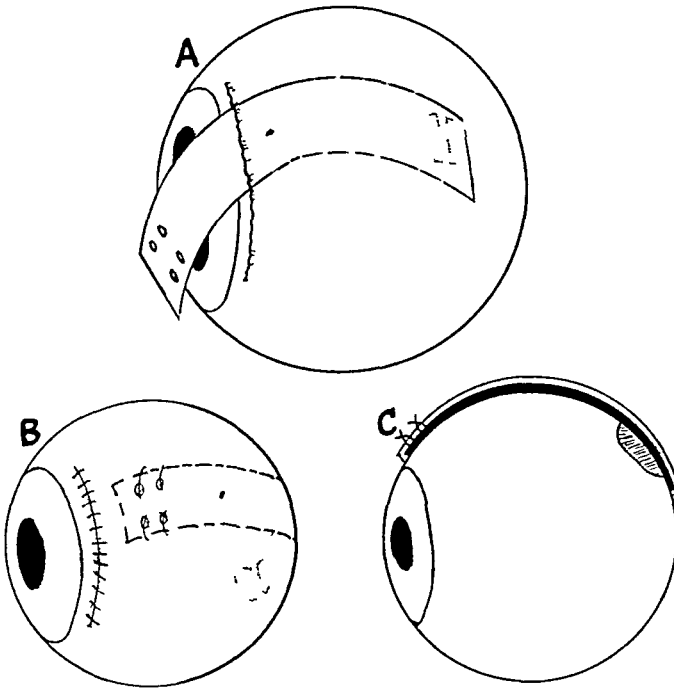


Fig 2—A, diagrammatic representation of the applicator with two radon seeds being inserted under the conjunctiva and Tenon's capsule B, diagrammatic representation of the applicator with two radon seeds in place, "buried" under the conjunctiva and Tenon's capsule and sutured to the sclera C, diagrammatic representation of the lateral view of the applicator in place, "buried" under the conjunctiva and Tenon's capsule overlying the retinoblastoma and sutured to the sclera

The length of the band depends on the location of the tumor as measured from a fixed point on the eyeball (e g, the limbus) in a particular meridian. This applicator follows the contour of the eyeball (fig 2 *A*) and is "buried" (fig 2 *B* and *C*) under Tenon's capsule and the conjunctiva. Precautions are taken to avoid injury to muscles, vortex veins and other anatomic structures. The proximal

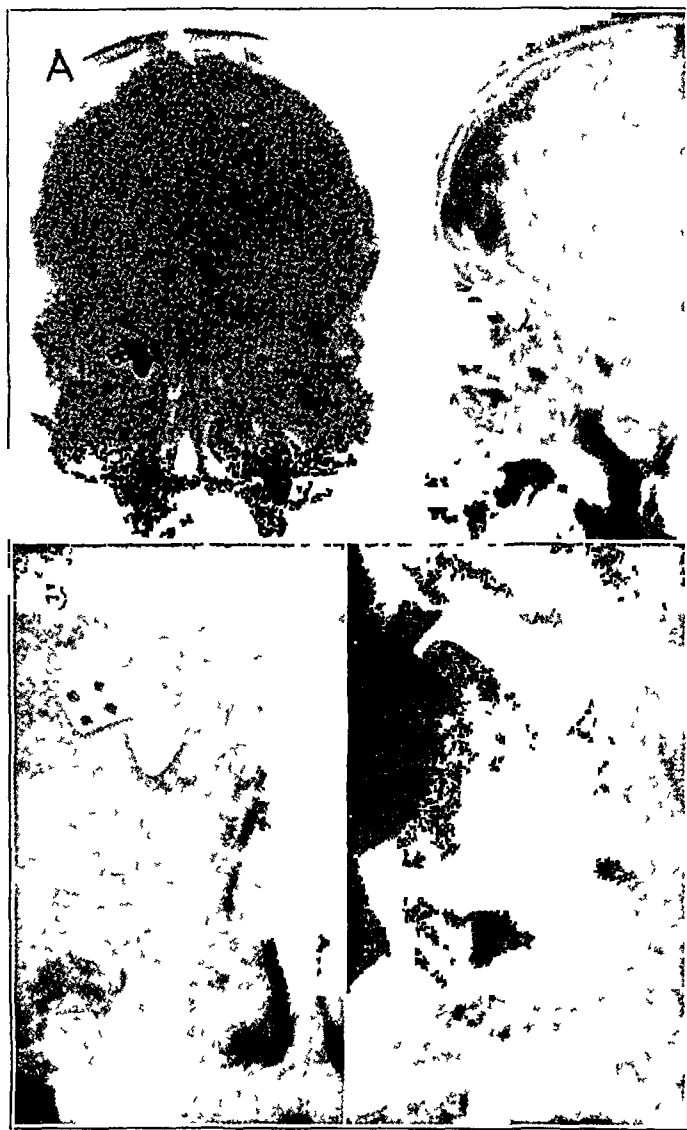


Fig 3—Anteroposterior and lateral roentgenograms (*A*, reduced, and *B*, slightly enlarged), showing the applicator in place

end is sutured to the sclera from the fixed point of reference. The applicator (fig 3 *A* and *B*) with the radon seeds is left in situ for the desired length of time. Then the appliance is removed with the seeds in place by opening the conjunctiva at the proximal end and reclosing it. Thus, the possible difficulties encountered in suturing at the posterior parts of the eyeball are eliminated. The reaction caused by the applicator itself is negligible. The application of radon

seeds may thus be repeated at such intervals, and in such doses, as are deemed necessary for the proper treatment of the tumor

We are in accord with the conclusions of Martin and Reese that the method of treatment for bilateral retinoblastoma should be enucleation of the more involved eye and fractionated radiation therapy of the other, if there is a chance to control the disease and conserve vision and if the technical facilities are available

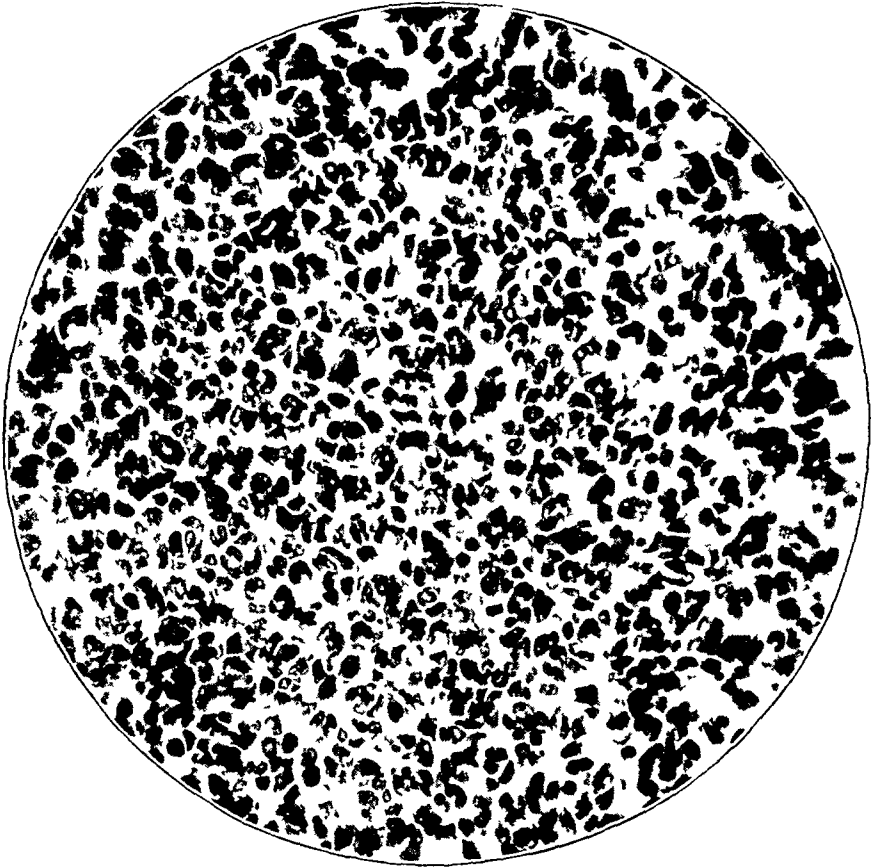


Fig 4—Retinoblastoma from the enucleated left eye,  $\times 400$ , hematoxylin and eosin stain

#### REPORT OF CASE

E C, a white boy aged  $13\frac{1}{2}$  years, was first seen in the children's clinic, Jefferson Medical College Hospital, on March 20, 1934, at the age of 1 month. The diagnosis was hypospadias. The child had had a normal birth. Three other children were living and well, there was no familial ocular disease. The patient was brought to the eye dispensary on Jan 22, 1935, at the age of 10 months, because his mother noticed a grayish reflex from the left eye ("cat's eye reflex"). She stated that at the age of 2 months she noticed an occasional "turning in" of the left eye, which was not present at the time of admission. This grayish spot had increased in size in the last two months. There was no history of injury or of

acute infection The eyes had never been red Examination revealed that the eyelids, rotation, tension (right eye, 18 mm, left eye, 18 mm [Schiotz]), conjunctiva and pupillary reactions to light and in convergence were normal With oblique illumination, a grayish white reflex was obtained in the left pupil Ophthalmoscopic examination was done with the patient under a general anesthesia The media and the fundus of the right eye were normal Almost the entire posterior segment of the left eye seemed to be filled with a grayish white growth, somewhat irregular in contour and studded here and there with tiny blood vessels which showed up easily by contrast with the white background No other details were seen The diagnosis of retinoblastoma was made The patient was seen by several members of the staff

Enucleation of the left eye was performed on January 29 No implant was used Roentgenograms of the skull and chest and all the long bones revealed no evidence of any metastatic change The blood count, serologic tests and urinalysis gave normal results The pathologic report was retinoblastoma (fig 4) .

On March 27, 1935, 50 mg of radium in a small pack was applied for thirty minutes to the region of the left temple

*Subsequent Course*—Dec 12, 1935 Right eye The media and fundus were normal Left eye The socket was clean

May 13, 1938 Right eye The external appearance was normal, the pupil reacted normally to light and in convergence Ophthalmoscopic examination with the pupil dilated revealed that the media were clear, the disk oval, the color good, the cup slightly full and the margins somewhat blurred, no lamina cribrosa was seen the vessels were generally normal About 4.5 to 5 disk diameters from the nasal margin of the nerve, in the 1.30 o'clock meridian, was a silver gray mass, elevated 1.25 D, which was 2 disk diameters long and 0.5 disk diameter wide and lay in a fork of the superior nasal vein The mass was roughly triangular, with the apex at the vessel Smaller vessels were seen to cross over and lie directly on the growth There was no evidence of pigmentary disturbance or hemorrhage in the involved area (fig 5) The macular area and the rest of the fundus appeared normal

Left eye The socket was clean

A course of roentgenotherapy for the retinoblastoma of the right eye was decided on

Oct 26, 1938 The size and height of the tumor were slightly increased Below it were two small, dark red areas of retinal hemorrhage, each about 0.25 disk diameter in width

Nov 15, 1938 Vision was 6/9, 1 radon seed (2.5 millicuries), embedded in dental stent, was sutured in place on the sclera overlying the growth for 113.75 millicurie hours Then one application of 1 radon seed and three applications of 2 radon seeds (2.5 millicuries each) were made during the period up to November 1939 The retinoblastoma gradually disappeared Pigmentary and retinochoroidal changes with beginning irradiation cataract (the latter appearing eighteen months after the first treatment) developed during this period

April 1942 It was thought that three tiny silvery areas with punctate retinal hemorrhages in the 11.30 meridian, 2 disk diameters above the nerve, were evidences of new growth

May 1, 1942 Three 2.5 millicurie radon seeds were applied in this area

May 10, 1943 Vision was 20/70 in the right eye with correction, the fundus was free of growths

Jan 29, 1944 Vision was 20/100 in the right eye with correction

March 15, 1946 Vision was 5/60 in the right eye with correction. A detailed study of the fundus was difficult because of the extensive changes in the lens (irradiation cataract). The macular area was now extensively spotted with small retinal hemorrhages and bright, sharply defined, yellowish white areas with delicately pigmented borders, which resembled somewhat part of a macular "star." Extensive changes were noted in the retina and choroid in the upper central and temporal areas. Here the choroidal circulation was clearly visible, and brown, dustlike pigmentary changes were observed over an extensive mottled area. The original area of choroidal atrophy in the upper nasal quadrant remained unchanged.

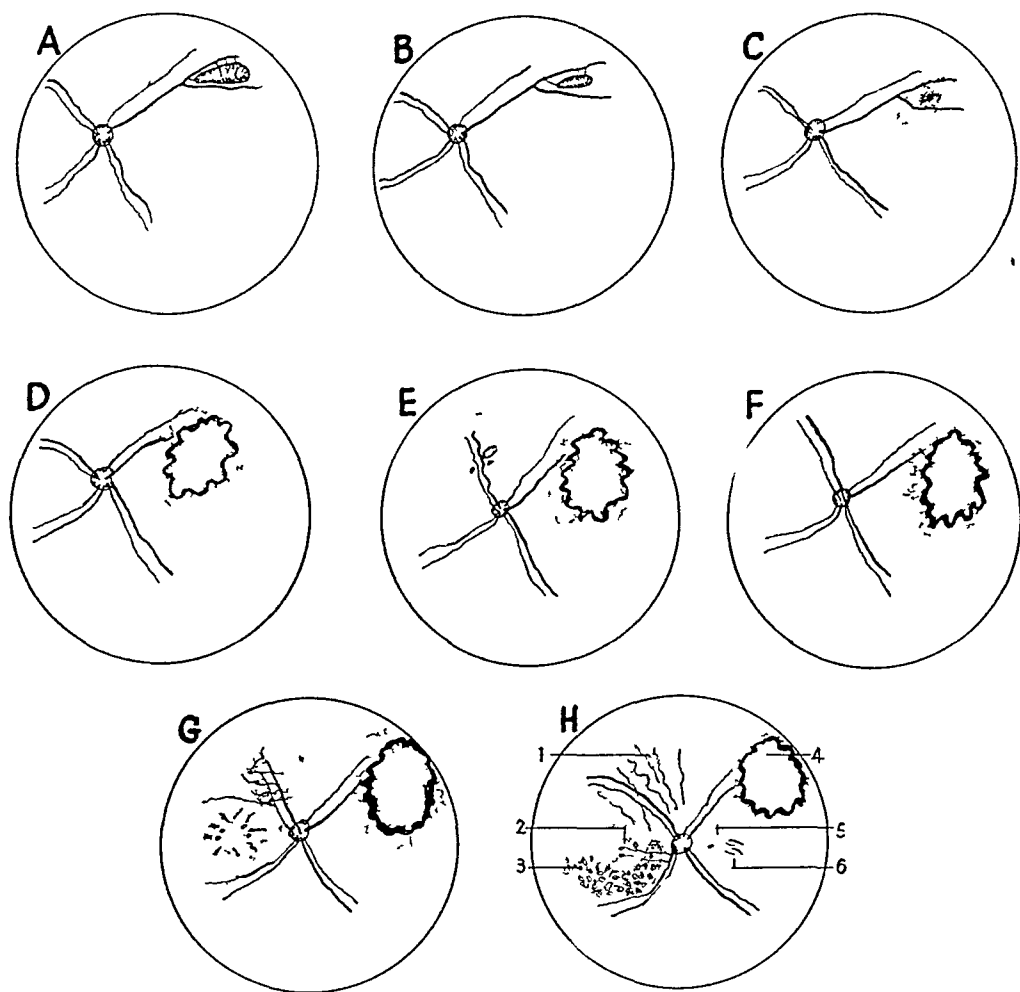


Fig 5—Diagrammatic representations of the retinoblastoma in the right eye, as seen chronologically

*A* (May 13, 1938), original appearance of the retinoblastoma, *B* (Sept 28, 1939), after two applications of radon seeds, *C* (Nov 27, 1939), after five applications of radon seeds, *D* (November 1940), after five applications of radon seeds, *E* (April 21, 1942), just before the sixth application of radon seeds, *F* (December 1942), approximately seven months after the sixth application of radon seeds, *G* (March 15, 1946), *H* (1947), showing (1) choroidal vessels and dustlike brown pigment, (2) miliary aneurysms, (3) area resembling circinate retinitis, (4) area of choroidal atrophy, (5) silvery bodies and (6) punctate and fine linear hemorrhages

There was a partial symblepharon in the upper nasal fornix at the site of the previous operations. The bulbar conjunctiva in this area was pigmented, with increase in vascularization and a tiny telangiectatic spot, about 1 mm in diameter, in the extreme upper temporal fornix. Examination with the slit lamp revealed a few punctate, brown endothelial dots and a small, tongue-like projection of vascularized conjunctiva 1 mm to the side of the cornea, at 1 o'clock, with slight increased capillarity at the upper limbus. The aqueous and iris were normal. Changes in the lens due to irradiation were more advanced than on previous examination. There had been no pain or discomfort in the eye since the last application of radon, in May 1942. No rise of intraocular tension was noted throughout the course of treatment.

Nov. 4, 1946. The patient went to the Overbrook School for the Blind and was learning Braille. Vision was 6/60 in the right eye without correction and was not changed with correction, the media and fundus were unchanged, biomicroscopic examination revealed no change since the previous examinations.

March 10, 1947. External examination revealed essentially the same condition as before. Beginning at the temporal border of the nerve, and extending in a comet-shaped area, was a golden yellow area, resembling the lacelike pattern of circinate retinitis. It stood out in sharp contrast to the darker macular area and the rest of the fundus. In the macular area itself were numerous tiny aneurysms and capillary dilatations involving primarily the venous branches. Above the macular area, the fundus was somewhat mottled and faded, with some absorption of pigment and seemingly covered with brown, powdery pigmentation. The old atrophic area in the upper nasal quadrant noted previously was slightly elevated (?) because of proliferation of fibrous tissue. About 15 disk diameters from the nasal border of the nerve were a series of minute capillary dilatations, resembling punctate hemorrhages. In this cluster were a few faint, woolly, silvery, dark areas. Here and there throughout the fundus some of the veins showed sausage-like constrictions. Vision was 6/60 without glasses with undilated pupil, as tested on three different charts.

Oct. 15, 1947. Right eye. Under cycloplegia with 1 per cent atropine sulfate, a correction of +1.25 D  $\subset$  +2.00 cyl, axis 90 gave vision of 6/60. Tension (Schiotz) was 19 mm (seen by Dr. William Zentmayer). The changes in the lens and the condition of the fundus were essentially as noted on previous examination. Biomicroscopic examination revealed slightly increased vascularity in the upper nasal limbus, the cornea was otherwise normal, the aqueous was normal, and the iris appeared as before, irradiation cataract persisted.

*Résumé of Operations on the Left Eye*—1. Enucleation, on Jan. 29, 1935, was followed by radium therapy on March 27, 1935, 15 mg. in a small pack was applied to the left temple for thirty minutes. The pack consisted of 10 needles in a monel<sup>®</sup> metal covering 0.3 mm thick, each needle containing 5 mg. of radium. These were placed in a lead box (dimensions not available) with an ordinary blotter and a layer of ordinary adhesive tape for filter on the surface next the skin.

2. Five applications of radon seeds in a special holder and 1 radon seed embedded in dental stent, for a total of 3,760 millicurie hours, were given between November 1938 and May 1942.

*Roentgen Treatment of the Right Eye*—First Series (May 18, 1938 to June 10, 1938) The factors were as follows dose, 200 kilovolts, distance, 50 cm (laterally) to the temporal side, filter, 0.5 mm of copper and 1 mm of aluminum The first treatment was 64 r, and each treatment thereafter, 160 r, for a total of 1,504 r

Second Series (July 28, 1939 to August 24, 1938) A total of 1,600 r was given, making a grand total of 3,104 r

#### SUMMARY

A patient with retinoblastoma (verified by microscopic and gross study of the enucleated eye) has been treated and observed for twelve years Retinoblastoma in the remaining eye has been treated, with cure for a period of nine years (1938)

Enucleation of one eye was performed in 1935, when the patient was 18 months of age The optic nerve was microscopically free of tumor cells

Roentgenotherapy to the right eye was given as outlined here It will be noted that the total of 3,104 r given was far below the dose advised by the fractionated method of Martin and Reese<sup>3a</sup> In November 1938, 25 millicuries of radon was applied in dental compound and sewed to the overlying sclera Five applications of radon seeds were used in the holder previously described<sup>6</sup> from March 1939 to May 1942

The patient was 10 months old when treatment was instituted and is 13½ years old at the time of this report Typical irradiation cataract and changes in the fundus, probably incidental to radon therapy, are described Visual acuity is 6/60 The patient attends a sight-saving school The changes in the lens, and perhaps the macular changes as well, may become more pronounced

In retrospect, the areas thought to be new growths in April 1942 may quite possibly have been a late reaction to the radon applied previously This condition has been noted and described by Martin and Reese<sup>2d</sup> in their large series treated by fractionated roentgen irradiation

#### CONCLUSIONS

We can do no better than endorse the procedure of Martin and Reese in the treatment of retinoblastoma (1) for unilateral ocular involvement, prompt enucleation with as long a section of the optic nerve as possible, and frequent ophthalmoscopic examinations for five years, (2) for bilateral involvement, prompt enucleation of the more diseased eye and radiation therapy, with the idea of saving life and

conserving vision in the remaining eye if the growth is not too far advanced and the specialized technic of fractionated roentgentherapy is available

For ocular and intracranial involvement of relatively easily accessible areas intracranial approach and excision of growths with enucleation are recommended

The local use of radon by the method described<sup>6</sup> is recommended as another form of treatment of this malignant disease, particularly when the exact and careful technic of fractionated roentgenotherapy described by Martin and Reese is not available



## MYDRIATICS

### A Clinical Observation

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THE PURPOSE of this paper is to evaluate the clinical merit of the commonly available mydriatics as to such factors as safety, speed of action and return to normal pupillary size

All drugs used in medicine have a range of dosage depending in part on the age of the patient and on whether the clinician desires the minimal or maximal effective dose for the patient in question. The same is true of drugs used in ocular diseases except that in ophthalmology particular care should be exercised when mydriatics are used. The initial evidences of overdosage of any drug are not usually disastrous, and the discontinuation of the drug ordinarily leads to complete return to normal in a short time. This tendency does not prevail with mydriatics. The use of a mydriatic in a patient with "potential glaucoma" may terminate in a serious complication, with a blind eye as a result.

#### GLAUCOMA COMPLICATING THE USE OF MYDRIATICS

Occasionally there appears in the ophthalmologic literature the report of a case of glaucoma following the use of a mydriatic. H. Gifford<sup>1</sup> reported 11 cases of glaucoma which developed after use of a mydriatic, including that of a woman aged 21. Several of the audience present at the reading of his paper reported similar experiences with mydriatics. Gifford also reviewed the literature up to the time of the writing of his paper and mentioned accidental development of glaucoma following the use of cycloplegics, mydriatics and local anesthetics, such as duboisine, scopolamine, eucatropine, epinephrine and phenacaine. Horner and Bettman<sup>2</sup> reported a case of glaucoma following the administration of 1 drop of epinephrine bitartrate in a patient who had never had symptoms of glaucoma. Beach and Holt<sup>3</sup> reported 9 cases, with a range in ages of 19 to 70 years, which came under their observation. Their conclusion

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From the Eye Clinics of the Hospital of the Protestant Episcopal Church and St. Christopher's Hospital for Children.

1. Gifford, H. The Desirability of Using Miotics as Adjuvants to Mydriatics, *J. A. M. A.* **67** 112 (July 8) 1916.

2. Horner, W. D., and Bettman, J. *Am. J. Ophth.* **19** 311, 1936.

3. Beach, S. J., and Holt, E. F. *Am. J. Ophth.* **24** 668, 1945.

was that glaucoma is a rare condition, chiefly affecting women, that youth or the previous use of mydriatics is no bar to its development and that the attack is remedied quickly by strong miotics. They suggested a careful examination of the pupil and anterior chamber before a mydriatic is used. Goar<sup>4</sup> "spent an anxious half-day trying to contract a pupil in a patient with paredrine." He also operated on several patients in whom acute glaucoma developed after the instillation of epinephrine.

An unfortunate experience occurred in my practice.

Mrs. D. M., aged 32, came for an examination of the eyes on Feb. 16, 1931, at 5 p. m. (the conclusion of office hours). She was told that there was no time then for a complete examination, but that a drop of medicine (1 per cent homatropine hydrobromide U. S. P.) would be instilled for examination of the fundus. She was to return the next day to complete the refraction. Her irises were brown and the anterior chambers normal, and the pupils reacted to light. The fundi were normal. She was not asked whether she saw halos. The procedure to be followed the next day would have been that observed in other cases, namely, instillation in each eye of 1 drop of homatropine hydrobromide, 1 per cent, at ten minute intervals for six doses. She did not report for examination the next morning, but on the evening of February 17 she called to say that she had had a gastric upset and a headache all day, which localized itself in a severe pain over the eye, and that her vision was dim. She was advised to go to the hospital immediately, where it was found that she had tension of 40 mm. in the right eye and of 50 mm. in the left eye. The blood and basal metabolic rate were normal, transillumination showed normal fundi, and a roentgenogram of the orbits revealed nothing remarkable. Physostigmine sulfate was used immediately, without effect. On the afternoon of February 19, an iridectomy was performed on both eyes, with resultant vision of 20/100 and 20/50. She was under continuous care for several months after this. Up to the present time she has never had a recurrence of the condition, and her vision is unchanged.

Aside from the rarity with which glaucoma follows the use of mydriatics, the ophthalmologist is thrown off his guard by the frequency of administration of strong mydriatics, such as the employment of atropine in maximum and frequent doses, regardless of the age of the patient, for the cure of corneal ulcer. If any complication takes place, it is oftener dermatitis rather than glaucoma.

In a desire to shorten the period of inconvenience of mydriasis, ophthalmologists have used powerful mydriatics with cycloplegic quality often, yet glaucoma has not been reported. Some investigators have used 1 or several drops of the mydriatic itself, and some have added a synergist.<sup>5</sup> Vandiver<sup>6</sup> dusted a small quantity of homatropine

<sup>4</sup> Goar, F. L. *Tr. Am. Acad. Ophth.* **46** 19, 1941.

<sup>5</sup> Beach, S. J. *Connecticut M. J.* **4** 140, 1940, *Tr. Am. Acad. Ophth.* **42** 179, 1937. Beach, S. J., and McAdams, W. R. *Am. J. Ophth.* **21** 121, 1938. Marron, J. J. *Cycloplegia*, *Arch. Ophth.* **23** 340 (Feb.) 1940. Moncrieff, A., and Schriebl, R. J. *Am. J. Ophth.* **24** 282, 1941. Sudranski, H. F. *Evaluation of Homatropine-Benzedrine Cycloplegia*, *Arch. Ophth.* **20** 585 (Oct.) 1938. Tait,

powder into the eye and repeated the procedure if necessary. Hartshorne<sup>7</sup> used a cycloplegic with patients of 45 or 50 and cited Wiggers as never doing a refraction on a patient up to, or even over, 60 years of age without a mydriatic. The author specifically stated that in his cases he used a miotic to follow up the mydriatic.

A discussion as to whether absolute cycloplegia is essential to good refraction, as cited by Friedman,<sup>8</sup> is not within the scope of this paper except to state that the cycloplegic property in a mydriatic possibly prolongs the time within which the mydriatic is eliminated. Therefore, in a selection of mydriatics the one with the least cycloplegic effect is most desirable.

It is generally conceded that a mydriatic will not cause glaucoma in an eye not affected by this disease. Some ophthalmologists even go so far as to state that the giving of a mild mydriatic in the case of a questionable "preglaucomatous state" is indicated as a diagnostic measure in definitely determining the condition. The rationale of such a procedure is questionable and has been discussed by such an authority as Gradle.<sup>9</sup>

#### PRELIMINARY STUDY OF MYDRIATICS

To begin this study, it was necessary to establish an arbitrary minimal size to which all pupils must be dilated. Ordinarily, some eyes may be examined without any mydriatic, but it was felt, after questioning many ophthalmologists, that a pupil of 7 mm would permit a thorough examination of the fundus, as well as make it possible to use the slit lamp effectively. With such dilations, one may avoid any errors of omission, such as may occur in the examination with an undilated pupil.

For the study of the relative efficiency of mydriatics, a group of drugs had been selected. The most suitable drug would be one which opened the pupil fastest and painlessly, with no untoward symptoms, and which could most easily be counteracted by the use of a mild miotic. In a previous, unreported, series of several thousand patients who had 1 to 3 drops of 1 per cent physostigmine salicylate instilled in the eyes every fifteen minutes until miosis was fully established, 2 patients became very faint, so that they had to lie down and stimulants had to be administered. One of these patients was almost pulseless. This condition was possibly brought on by the intense spasm of ciliary muscles and the violent pulling sensation which the patient experienced.

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J. H. J. Iowa M. Soc. **32** 162, 1942. Thorne, F. H., and Murphy, H. S. Cycloplegics, *Arch. Ophth.* **22** 274 (Aug.) 1939. Weinman, F. B., and Fralick, F. B. *Am. J. Ophth.* **23** 172, 1940.

6 Vandiver, H. F. *J. Oklahoma M. Soc.* **33** 15, 1940.

7 Hartshorne, I. *Eye, Ear, Nose & Throat Monthly* **19** 201, 1940.

8 Friedman, B. Comments on Teaching of Refraction, *Arch. Ophth.* **23**, 1175 (June) 1940.

9 Gradle, H. S. *Am. J. Ophth.* **30** 7, 1946.

To avoid such a reaction, the miotic chosen for this study was pilocarpine hydrochloride in 1 per cent solution. Five drops was used at each instillation every few minutes until the pupils closed down to 2 mm or less. The mydriatic was permitted to expend itself without the assistance of a miotic in some cases (table).

In some cases the miotic had a meager, or no, observable effect, as in the case of homatropine and "eumydrin" (atropine methylnitrate). Patients were examined for mydriasis at various times of the day to see whether at certain periods better results were obtained in the dilation of the pupil.

Middleton and Chen<sup>10</sup> showed that in the study of cocaine, eucatropine and ephedrine the best mydriatic reaction was obtained with Caucasians, the next with Chinese and the poorest with Negroes. There is even an individual variation when a mydriatic is used on noses of the same color of different patients of the same age. It was unfortunate that of the patients studied all were of the white race, with the exception of 1 Japanese and 2 Negroes, but the relative intractability of the heavily colored iris in white persons was often observed.

The studies began in the latter part of November 1946 and continued for about ten months. Of the drugs considered for this type of study, three were unobtainable, viz., benzilyloxyethyl-di-methylethylammonium chloride, known commonly as E 3, the clinical use of which was described by Riddell<sup>11</sup> and Mann<sup>12</sup>, the Russian mydriatic platyphylline, and "veritol" (para-hydroxyphenyl-isopropylmethyl amine) formate, described in the German literature. The last two are mentioned in the United States Dispensary, twenty-third edition.

Avoided in these studies was "mydracaine,"<sup>13</sup> a preparation of atropine, cocaine and epinephrine, given subconjunctivally, and much too powerful for ordinary needs in ophthalmic practice.

Several drugs were not used in this study, for reasons to be stated. Synthetic epinephrine bitartrate<sup>14</sup> was discarded early because of its undesirable reaction. This white powder dissolves easily in buffer solution and makes a crystal clear 2 per cent solution, which after several weeks becomes dark brown, when it is considered useless. My experience with this drug was unpleasant in several cases. In these instances, a few minutes after its use, the sclera became blanched, the hands began to tremble, a cold sweat covered the face and the patient

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<sup>10</sup> Middleton, S. S., and Chen, K. K. *J. Pharmacol. & Exper. Therap.* **36**: 429, 1929.

<sup>11</sup> Riddell, W. J. B. *Brit. J. Ophth.* **30**: 7, 1946.

<sup>12</sup> Mann, I. *Brit. J. Ophth.* **30**: 8, 1946.

<sup>13</sup> Flynn, F. *Brit. J. Ophth.* **17**: 298, 1933.

<sup>14</sup> The drug used was "suprarenin," a brand of epinephrine (synthetic) bitartrate powder.

# Mydriatics

Synthetic substances allied to the alkaloids of the belladonna group	Number of Patients	Number of Patients	Age Range, Yr	Number of Drops Required					Size of Pupil, Mm			Color of Iris		Time to Reach Maximum Mydriasis, Min		Tension	Light Reflex Absent, %	Type in Full Mydriasis, as is, %	Time Taken to Contract Pupil		Read 37 M	Eye Cleared				
				1	2	3	4	5	6+	7 to Full	None	Gray	10	15	20 to 180				Spon taneous	With 1% Pilo carpine						
Homatropine hydrobromide, 1%	48	28	7 75	38	8	2	2	2	2	4	5	6 D*	4	28	10	15 to 105	Some high normal	38	46	11 to 48 hr	No effect		60 to 180 min			
"Syntropan," 6%	56	33	4 79	36	15	2	1	2	1	1	9	80	12	29	15	20 to 180	High normal	29	89	5 to 9 hr	30 to 127 min					
Atropine methylnitrate	48	23	3 32	17	24	7	2	96	0	28	11	23 to 165	Some high normal	25	25	100	None tried	2 to 8 hr	25 to 60 min							
Eucatropine hydrochloride, 1%	12	8	20 71	3	3	4	1	2	7	25	4	5	3	20 to 60	Normal	None	100	None	At once							
Eucatropine hydrochloride, 2%	61	44	13 80	11	23	19	5	2	1	1	3	13	72	11	32	18	40 to 105	Normal	7	100						
Parasympatholytic Drugs																										
Dibutoline sulfate, 5%	104	57	3 77	56	34	13	1	1	4	95	24	53	27	20 to 180	Normal	94	7	16 to 48 hr	90 to 390 min		No clearing period					
Sympathomimetic drugs																										
Paredrine, 1%	78	47	9 71	35	27	9	6	1	6	9	81	25	35	18	20 to 115	Normal	6	100	Clear next a m	8 to 70 min		1 1/2 to 5 hr				
Paredrine, 3%	108	72	8 80	74	12	13	3	3	13	5	21	64	21	62	25	20 to 128	Normal	21	17	Clear next a m	20 to 80 min		1 to 5 hr			
Phenylephrine hydrochloride, 2.5%	41	31	8 80	21	12	8	2	1	3	6	80	11	14	19	20 to 180	High normal	91	86	70 to 120 min	10 to 100 min		No clearing period				
Synergistic drugs																										
Racépedrine and homatropine	10	5	7 65	2	4	3	1	5	1	4	0	1	9	None reached, full mydriasis	Normal	20	30	6 hr	None used							
Ephedrine and homatropine	41	25	7 71	16	17	7	1	2	3	2	83	19	20	2	20 to 180	Normal	44	39	2 1/2 to 19 hr	15 to 120 min		1 1/2 to 10 hr				
Racépedrine and eucatropine	53	37	13 77	10	20	17	7	3	1	7	2	9	69	16	27	15	25 to 170	Normal	85	81	2 to 9 hr	15 to 180 min		1 to 5 hr		

\* Dilatation, expressed as a per cent

\* Dilatation, expressed as a per cent

became nauseated. In 2 of the cases several hours elapsed before a return to normal. After the use of this drug was repeated, these untoward symptoms lessened somewhat. The manufacturers are aware of these shortcomings and suggest that the patient be forewarned. The advisability of using this preparation in the face of such secondary effects is questionable.

Hoerner and Bettman<sup>15</sup> and Post<sup>16</sup> stated that 1 per cent cocaine with 1 per cent eucatropine hydrochloride U. S. P. is desirable as a mydriatic because this combination can be counteracted more easily and less painfully, but the combination has a tendency to increase intra-ocular tension in the normal eye of elderly persons, and the pupil hardly approached the diameter of 7 mm which was arbitrarily established.

Howard and Lee<sup>16</sup> used epinephrine hydrochloride. They claimed, however, that a stinging sensation, headache and nausea were associated with its use. In this study ephedrine was used only with homatropine hydrobromide (table), for reasons to be explained later.

Cocaine was not used on account of the occasional corneal softening and the frequent corneal edema, which makes ophthalmoscopic and biomicroscopic examinations difficult.

#### TYPES OF DRUGS STUDIED

The mydriatics studied may be arbitrarily divided into four groups.

1 Synthetic substances allied to the alkaloids of the belladonna group<sup>17</sup>

Homatropine hydrobromide, 1 per cent

Atropine methylnitrate ("eumydrin"), 1 per cent

Eucatropine hydrochloride, 1 per cent

Eucatropine hydrochloride, 2 per cent

"Syntropan," (the phosphate of 3-diethylamino-2,1-dimethylpropyl esters of tropic acid), 6 per cent

These drugs, like atropine, are all optically racemic. Unlike atropine, however, which occurs in nature, the drugs studied are all synthetic preparations. The more powerful mydriatics with definite cycloplegic properties, such as atropine, scopolamine and duboisine, were not used in this study, for obvious reasons.

#### 2 Choline esters

Dibutoline sulfate, 5 per cent (dibutylcarbamate of dimethylethyl- $\beta$ -hydroxyethyl-ammonium sulfate)

<sup>15</sup> Post, L. T. *Am J Ophth* **20** 33, 1937

<sup>16</sup> Howard, H. J., and Lee, T. P. *Proc Soc Exper Biol & Med* **24** 700, 1926

<sup>17</sup> Goodman, L., and Gilman, A. *The Pharmacological Basis of Therapeutics* New York, The Macmillan Company, 1941, p. 462

### 3 Cholinergic drugs

"Paredrine hydrobromide ophthalmic" (1 per cent solution of *p*-hydroxy- $\alpha$ -methylphenylethylamine hydrobromide in distilled water, made tear isotonic with 2 per cent boric acid and preserved with merthiolate, 1:50,000)

"Paredrine hydrobromide" (*p*-hydroxy- $\alpha$ -methylphenylethylamine hydrobromide), 3 per cent

Phenylephrine ("neo-synephrine") hydrochloride, 2.5 per cent

4 Drugs of group 1 augmented by the synergistic action of either ephedrine or racéphedrine (*racemic*-1-phenyl-2-methylaminopropanol-1)

Ephedrine hydrochloride, 1 per cent, and homatropine hydrobromide, 1 per cent

Racéphedrine hydrochloride, 1 per cent, and homatropine hydrobromide, 1 per cent

Racephedrine hydrochloride, 1 per cent, and eucatropine hydrochloride, 1 per cent

Although it is felt by some investigators that a low  $p_H$  tends to better results in the use of mydriatics, de Cori and Wiechmann<sup>18</sup> reported that a shift in the  $p_H$  to the alkaline side increases the speed and efficiency of both mydriatics and miotics. Thus, with the exception of preparations coming already prepared, such as dibutoline sulfate and phenylephrine hydrochloride, all the solutions used in the series were prepared in a boric acid-sodium borate ("borax") buffer with a  $p_H$  of 7.0 to 7.3.<sup>19</sup>

### TECHNIC

All mydriatics were instilled at 12 o'clock at the limbus with the head of the patient tilted backward or with the patient lying down. The mydriatic was allowed to flow slowly over the surface of the cornea, and the eyelids were kept open for about one-half minute. In the case of a young patient it was impractical to have him lie down while the drops were inserted, since the child became apprehensive and did not cooperate well. For a similar reason, it was not possible to obtain the intraocular pressure in patients of the younger group. In much the same way, some of the older patients were not very cooperative in tests for cycloplegia. The eyes of the patient were observed every ten to fifteen minutes; additional drops of the mydriatic were instilled only when the pupils during these intermittent examinations showed no tendency to further dilation. The droppers<sup>20</sup> used in this study were of the "clinical type," with which each drop weighed the same. The same mydriatic was used in the two eyes except when otherwise stated.

Bothman<sup>21</sup> showed that many of the ill effects of strong cycloplegics were obtained by absorption of the drug through the tear duct, and it is now generally recognized that there is less absorption of the mydriatic when the lacrimal puncta

18 de Cori, R., and Wiechmann, R. Read at the Fifteenth Meeting of the International Congress of Ophthalmology, Dec 8, 1937, abstracted, *Arch Ophthalmol* 20:145 (July) 1938.

19 Feldman, J. B.  $p_H$  and Buffers in Relation to Ophthalmology, *Arch Ophthalmol* 17:797 (May) 1937.

20 Phenylephrine and dibutoline are dispensed with their own droppers. In the case of dibutoline solution, the drops are smaller than the others used in this study, 21½ drops from the dibutoline bottle equals 0.5 cc. This is equivalent to 15 drops from the "clinical dropper."

21 Bothman, L. *Tr Am Acad Ophthalmol* 42:164, 1937.

are compressed. However, in this group, no attempt was made to compress the tear duct. It was felt desirable to see what untoward symptoms would arise by nasal absorption of the drugs used.

The mydriatics were used at room temperature. The instillation of the mydriatics and miotics, as well as the observations, were made by myself.

For each patient were recorded the name, age, sex, time of day at which the drop was inserted, time when successive drops were used, progress of mydriasis and resultant dilatation of from 7 mm to maximum diameter. Also noted were the approximate size of the anterior chamber, the color of the iris and the diameter of the pupil when the instillations were begun. When obtainable, the ocular pressure was procured before the mydriatic was instilled and again at the maximum dilatation. The progress of the miosis with pilocarpine hydrochloride was noted, and such other comments as were deemed essential in the analysis of the cases were made. The intraocular pressure was taken with the use of 1 per cent butacaine sulfate U S P ("butyn sulfate"). A Schiötz tonometer was used.

None of the patients had synechias. In each patient, the pupils reacted to light and in accommodation. All measurements of pupillary diameter were made in the same room with equally diffused light. A pupillometer with a Venier device for accuracy was used. When the drops were flicked out, the case was discarded.

Since it is desirable that at least in such a subjective test as that for cycloplegia in which the Prince rule is used the refraction be as nearly correct as possible, each patient came for several visits for perfection of his refraction prior to the mydriatic study. Some of the adults were illiterate or irresponsible or had cataracts, and were therefore unsuitable for this test.

When the pupil was maximally dilated for the individual subject, an effort was made to see whether there was a pupillary reflex and whether the patient could read 37 M type. Glasses were used here if there was a refractive error.

It was frequently found that the time consumed in contracting the pupil with pilocarpine after full mydriasis was seldom as long as the time necessary for maximum dilatation. This may have been due to the fact that more drops of 1 per cent pilocarpine nitrate were used at each instillation (5 drops of miotic against 1 drop of mydriatic) and that the miotic was more frequently instilled than the mydriatic (about every five minutes, regardless of the degree of pupillary contraction).

Except for severe burning after the instillation of a few mydriatics, some subconjunctival injection following the instillations of pilocarpine and the experience with epinephrine bitartrate, no complications were observed, and the corneas were all clear.

Cycloplegia was checked with the correct refraction worn. In addition, a +3 D lens was placed before each eye, together with a 3 mm disk opening to compensate for the fully dilated pupil. The patient was required to read the 37 M type. There were several shortcomings in this test with respect to the present study: (1) The test was subjective, so that the validity of the patient's answer was questionable, and (2) the test for cycloplegia was made at the height of mydriasis, which may have been obtained before cycloplegia set in.

#### MYDRIATICS

*Homatropine Hydrobromide, 1 Per Cent*—Homatropine hydrobromide was the first mydriatic studied in this series. Only 1 per cent of the drug, dissolved in buffer solution,<sup>19</sup> was used. It was deemed desirable to use the weakest dilution of the mydriatic selected which would prove effective in dilating the pupil maximally.



This drug comes prepared in powder form or in soluble  $\frac{1}{2}$  grain (0.032 Gm.) tablets. It is a synthetic preparation allied to the belladonna alkaloids. This mydriatic differs from atropine in that it is derived from a tropine base and mandelic acid, while atropine is derived from tropic acid.<sup>17</sup>

Forty-eight patients were examined, the ages ranging from 7 to 75 years, the majority of the patients were under 35 years of age (table). Forty-four patients obtained maximum dilatation of the pupil. One exceptional patient obtained maximum dilatation in fifteen minutes. Wolf and Hodge<sup>22</sup> gave the time for maximum cycloplegia with homatropine at between thirty and ninety minutes. With a patient obtaining full dilatation in fifteen minutes, one can understand how a test for cycloplegia would not be valid.

Only in 2 cases would a determination of the intraocular pressure be permitted by the patient. Both had normal tensions. With the pupil fully dilated, about one third of the patients did not have a light reflex, and about one-half could not read 37 M type with their corrections. Seven to 11 drops of pilocarpine hydrochloride, 1 per cent, had no immediate pronounced effect on the pupils, but shortened the period of mydriasis, in some cases to eleven or twelve hours. Ordinarily, the pupil returned to normal diameter in about two days.

*Atropine Methylnitrate* ("Eumydrin"),<sup>23</sup> 1 Per Cent.—This was the second of the synthetic substances allied to the alkaloids of the belladonna group to be studied. This mydriatic is optically racemic, as is atropine.<sup>17</sup> It is one-tenth as powerful as, and fifty times less toxic than, atropine.<sup>24</sup> As in the case of homatropine hydrobromide, 1 per cent pilocarpine hydrochloride was used to effect miosis, but was unsatisfactory. Since it was not known what complications might be expected with this mydriatic, which is seldom used, younger subjects were tested. The ages ranged from 3 to 32, and 48 patients were tested.

Forty-six patients obtained maximum mydriasis (table) in from twenty-five to one hundred and sixty-five minutes. Curiously, the shortest period of full mydriasis was twenty-five minutes, for a hazel-eyed patient, and the longest period was that for a child aged  $3\frac{1}{2}$  years.

While the percentage of dilatation was greater with atropine methylnitrate, it was often necessary to use 2 drops of this mydriatic to obtain

22 Wolf, A. V., and Hodge, H. C. Effects of Atropine Sulfate, Methylatropine Nitrate and Homatropine Hydrobromide on Adult Human Eyes, *Arch Ophth* 36 293 (Sept.) 1946.

23 This drug is also known under the names methylatropine, methylatropine nitrate and "metropine."

24 Pyle, W. L. An International System of Ophthalmic Practice, Philadelphia, P. Blakiston Son & Co., 1912, p. 176.

full mydriasis, whereas when homatropine was used the majority of the pupils dilated fully with only 1 drop

One exceptional patient went to the theater immediately after the examination and said he saw clearly. However, only about 25 per cent of the patients could read 37 M type during mydriasis, and an equal number had no light reflex. The pupils usually returned to normal in about two to three days, with 1 exception, of five days.

*"Syntropan," 6 Per Cent* — "Syntropan" is the third of the synthetic preparations akin to the belladonna alkaloids to be tested. It is the phosphate salt of the tropic acid ester of a tertiary amino alcohol<sup>17</sup>. It is believed to be one-thousandth as effective as atropine. Like atropine, it is optically racemic. This preparation is not in common use, but recently Bab<sup>25</sup> attempted to popularize this preparation, using a 6 per cent solution. He suggested that the vehicle be of a higher  $p_H$  than that of the mydriatics ordinarily used, in order to increase the degree of preservation. Personally, one feels that a mydriatic need not be made up in large quantities if its tendency to deteriorate is its only shortcoming.

Fifty-six patients were examined. The first study on this group was made with 27 patients. The powder is easily soluble, and a 6 per cent solution was at first made up in distilled water. The  $p_H$  of this solution was 4.9. The burning of the eye was intense. With the hope of possible alleviation of this stinging sensation, two other solutions were prepared, one in buffer solution of  $p_H$  6.1 and the other in a buffer solution of  $p_H$  7.0. Four patients were tested with the first solution and 4 with the second ( $p_H$  7.0) solution for both eyes. Both preparations were painful. To determine which of the two solutions was least disturbing, 21 patients were tested with a solution of  $p_H$  6.1 in the right eye and a solution of  $p_H$  7.0 in the left eye. As before, both eyes burned to an equal extent. It, however, must be said of 6 per cent "syntropan" that it is a powerful mydriatic, for in spite of the intense burning and the resultant dilution of the mydriatic with tears, 45 of the patients in this group obtained maximum mydriasis in from twenty to one hundred and twenty minutes.

The ages of the patients varied from 4 to 79 years. The greatest majority of patients obtained maximum dilatation after 1 drop was instilled (table). Less than a third of the patients did not have a light reflex under mydriasis, and few could not read 37 M type, possibly because of photophobia. The increase in tonometric readings averaged about 4 mm, a tension which was still within the high normal limits.

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25 Bab, W. Am J Ophth 29 728, 1946

*Eucatropine Hydrochloride U S P, 1 Per Cent*—Eucatropine was the last of the preparations of the alkaloids of the belladonna group. It is both synthetic and optically racemic. It is an ester of a piperidine derivative and mandelic acid. Sugar<sup>26</sup> expressed the belief that eucatropine does not dilate the pupil to a diameter sufficient to close the canal of Schlemm. Knapp,<sup>27</sup> however, reported 2 cases of glaucoma following the use of 7.5 per cent eucatropine hydrochloride.

All the pupils contracted with pilocarpine in from ten to sixty minutes. The tension showed a slight variation of 3 mm of mercury. All the patients could read with the pupil dilated, and in all the pupil reacted to light at its maximum dilatation.

*Eucatropine Hydrochloride U S P, 2 Per Cent*—Of the 61 patients in this group, 44 obtained full mydriasis. In a number of patients this was within forty-five minutes. However, for many patients from 3 to 7 drops of the mydriatic was required for the best dilatation (table). Pilocarpine contracted almost all the pupils. When no pilocarpine was used, two to eight hours elapsed before contraction took place. In 4 patients there was no light reflex, and all patients could read with the eye in mydriasis.

*Dibutoline Sulfate, 5 Per Cent*<sup>28</sup>—Under the name dibutoline, Swan and White<sup>29</sup> introduced a new choline ester which has mydriatic qualities. Since the authors<sup>30</sup> expressed the opinion that the dibutoline has an action similar to that of atropine (paresis of the sphincter muscle), and because they compared its action to that of homatropine, it was felt that this new drug could be included in this short study. Further encouragement was given by Peterson and Peterson,<sup>31</sup> who stated the opinion that the drug has a low toxicity even when administered in an increased dose over a prolonged period. The authors claimed that dilatation of the pupil parallels the amount of cycloplegia present. Examination of the present patients revealed no conjunctival irritation or superficial keratitis, such as was claimed by the authors to occur. There were no patients in this group on whom it was possible to check the bactericidal quality of this drug.<sup>32</sup>

It was suggested by the manufacturers that a 1 per cent solution of cocaine would enhance the action of dibutoline and that a single large

26 Sugar, H. S. *Am J Ophth* **24** 851, 1941.

27 Knapp, H. *Arch f Ophth* **29** 313, 1900.

28 This preparation is dispensed by Merck & Co., Inc., as "ophthalmic solution dibutoline 5%."

29 Swan, K. C., and White, N. G. *J Pharmacol & Exper Therap* **80** 285, 1944.

30 Swan, K. C., and White, N. G. *Proc Soc Exper Biol & Med* **53** 164, 1943.

31 Peterson, C. G., and Peterson, D. R. *Am J Ophth* **84** 236, 1945.

32 Swan, K. C., and White, N. G. *Di-N-Butylcarbaminoylecholine Sulfate*, *Arch Ophth* **31** 289 (April) 1944.

dose acted more effectively than repeated smaller doses given over a longer period. But the last two suggestions were not acted on in this study, since it was desired to compare dibutoline in a fair measure with the other mydriatics studied at this time.

One hundred and four patients were examined (table), 99 of whom obtained full mydriasis. The maximum time for spontaneous contraction of the pupil when dibutoline was used was usually less than that for either homatropine or atropine methylnitrate. In the case of each of the three drugs homatropine, atropine methylnitrate and dibutoline the maximum number of drops used to obtain full mydriasis was 3<sup>33</sup>. Only 17 patients would have the intraocular pressure taken, and, while the tensions for these subjects varied somewhat, all were within normal limits. Only 8 patients in this group could read 37 M type with the pupils fully dilated. In the majority of subjects no light reflex could be obtained. Data on the return of the pupil to normal with and without pilocarpine appear in the table.

*"Paredrine Hydrobromide"*—"Paredrine hydrobromide" is a sympathomimetic amine and is now introduced to supersede amphetamine, which it resembles in chemical structure. It was first synthesized in 1913, but became popular only within recent years.

*"Paredrine Hydrobromide Ophthalmic (1 Per Cent)"*—Of the 78 patients (table), 8 were from 70 to 74 years of age. The intraocular pressure varied, but was within the normal limits. Sixty-three of the patients obtained maximum dilatation with "paredrine hydrobromide ophthalmic." Almost all the patients could read 37 M type under mydriasis when their visual corrections were worn. Only a few patients had no light reflex. It was noted that when pilocarpine hydrochloride, 1 per cent, was instilled in the eye and the pupil became fully contracted, an artificial myopia developed. During this period the patient did not see clearly. It took from one-half hour to a maximum of five hours after instillation of pilocarpine for the myopia to disappear. In the majority of cases, however, the eyes cleared in two hours.

*"Paredrine Hydrobromide," 3 Per Cent*—This mydriatic in 3 per cent solution is difficult to obtain in the open market<sup>34</sup> at present, since its use is still in the experimental stage. One hundred and eight patients were tested. The drug was used with patients up to 80 years of age (table). Strangely, only 69 patients obtained full mydriasis, a poorer result than when the 1 per cent solution was used. It is interesting, however, to know that in using "paredrine hydrobromide" of stronger potency, when the patient did get maximum dilatation, the 1 per cent solution accomplished full mydriasis in fifty-two minutes, as

<sup>33</sup> One patient, an exception, obtained 4 drops (table).

<sup>34</sup> Smith, Kline & French Laboratories supplied this drug.

against forty-nine minutes for the 3 per cent "paredrine hydrobromide" Also, the greatest number of patients who received maximum dilatation with the 3 per cent solution did so with 1 drop of the mydriatic The eyes cleared in one to five hours, with an average of two and one-half hours In about one fourth of the patients the pupils did not react to light When no pilocarpine was instilled, the maximum time at which the pupil contracted was seldom longer than the next morning for patients examined in the afternoon However, some pupils contracted in from one to three hours Few patients of this group could read the 37 M type during mydriasis

Fortunately, in none of the patients studied did dermatitis venenata develop, as in the experience of Laval,<sup>35</sup> a complication which he claimed was rare

*"Paredrine Hydrobromide Ophthalmic," 1 per cent Versus "Paredrine Hydrobromide," 3 per cent*—For further comparison of the merits of these two mydriatics, 30 patients were studied, the 1 per cent solution being instilled in one eye and the 3 per cent solution in the other eye Either eye was used for the "paredrine hydrobromide," 3 per cent With the same number of drops, from one-half to one and one-half hours was required for 6 patients to obtain full dilatation in the eyes receiving the two strengths In the rest of the patients the pupil of the eye receiving the 3 per cent solution was from 2 mm larger than to twice the diameter of the pupil of the eye receiving the 1 per cent solution

#### GENERAL OBSERVATIONS

In using any of the mydriatics, it was interesting to observe a saturation point, especially in older subjects with hazel or brown eyes In these eyes no additional amount of mydriatic had any observable effect on the pupil after definite dilatation was obtained Indeed, in some cases the pupil was even observed to contract

Twenty-five patients were examined with the same and with other mydriatics on different days An inconsistency in the action of mydriatics was noted Thus, a mydriatic used on one day might dilate better, and in less time, than on another day

The increased activity of a mydriatic in rainy weather was noted in some cases Whether this is coincidental or whether the atmospheric conditions have any effect on the mydriatic is problematic It is possible that since the light is not intense on a rainy day, not so much light enters the dilated eye as on a sunny day, even though dark glasses are worn The action of the mydriatic is therefore undisturbed It was observed that placing the patient in a dark room after the mydriatic

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<sup>35</sup> Laval, J Allergic Dermatitis and Conjunctivitis from Paredrine Hydrobromide, Arch Ophth 26 585 (Oct) 1941

was instilled was more effective in dilating the pupil than using dark glasses in a well lighted room

*"Paredrine Hydrobromide," 1 per Cent Versus Eucatropine Hydrochloride, 2 per Cent*—Since these two mydriatics are relatively mild, it was felt that their comparison might be of value. Twelve patients were tested with 1 drop of one of these mydriatics in one eye and 1 drop of the other drug in the other eye. The ages of the patients ranged from 6 to 64 years. In 3 patients full dilatation was not obtained with either drug. In the other 9 patients the eye which received the "paredrine hydrobromide" was always 3 to 4 mm wider than the eye which received eucatropine.

*Phenylephrine Hydrochloride, 2.5 per Cent*—Phenylephrine ("neosynephrine") hydrochloride is a synthetic sympathomimetic compound, almost analogous therapeutically to epinephrine and ephedrine. It was the last of this group studied. The drug acts by relaxing the constrictor muscles of the pupil and strongly contracting the dilator muscle.

The solution when instilled in the eye stings quite a bit, even though a local anesthetic for ocular pressure has just been instilled.

Forty-four patients were examined in this group. Regardless of how much care was exercised in instilling the mydriatic, there was considerable dilution with tears. In spite of the burning and tearing, 35 patients obtained maximum mydriasis (table).

In many of these patients it appeared that the intraocular pressure coincided with the observations of Heath<sup>36</sup>, that is, the pressures were slightly increased, but were still in the high normal bracket. Pilocarpine effected a return to normal within several hours. This miotic usually caused some irritation and conjunctival injection, these symptoms, coupled with the prior instillation of phenylephrine hydrochloride, made the patient far from comfortable. Many subjects could read during mydriasis. A number had intense photophobia, making it difficult to determine a light reflex.

Glaucoma must be a rare complication when mydriatics are used. In a man aged 47, 7 drops of both 1 and 3 per cent "paredrine hydrobromide" followed by 1 per cent homatropine hydrobromide was used in both eyes over a period of four hours before a 7 mm pupil was obtained. The tension was taken after each instillation of the mydriatic, without any serious rise of ocular pressure.

In another case, a woman aged 61 had incipient changes in both eyes. She had a shallow chamber, her pupils reacted poorly to light, she did not complain of halos. It was explained to her that the drops might precipitate glaucoma but that a good view of the fundus was of

<sup>36</sup> Heath, P. Neosynephrin Hydrochloride, Arch Ophth **16** 839 (Nov) 1936

value in diagnosis. She agreed to use of the mydriatic, and 5 drops of phenylephrine was instilled during a period of one hundred and thirty-five minutes. The most that could be obtained was 6 mm of dilation for both eyes. Her ocular pressure was 4 mm higher during dilation, but was within normal limits. The phenylephrine did not produce any deleterious effect. She was the only patient who received as many as 5 drops of phenylephrine and yet had no after-effects.

*Phenylephrine Hydrochloride, 2.5 per Cent Versus "Paredrine Hydrobromide," 1 and 3 per Cent*—In the comparative study of phenylephrine hydrochloride, 2.5 per cent, and "paredrine hydrobromide," 1 per cent, only 3 subjects were studied. Only 1 subject obtained maximum dilation with both mydriatics. In the other 2 patients maximum dilation was obtained only with phenylephedrine hydrochloride.

It was felt that the 3 per cent "paredrine hydrobromide" was the concentration more comparable to the 2.5 per cent phenylephedrine hydrochloride, and its effect in 14 patients was checked. In 7 patients both drugs obtained maximum dilatation in about the same time. In the other 7, it appeared that the eye which received the 3 per cent paredrine hydrobromide obtained maximum dilation in less time.

*Homatropine Hydrobromide and Racéphedrine Hydrochloride*—In 1932 Hartlieb<sup>37</sup> published an article in the German literature describing the use of a mydriatic first suggested by Sattler. This consisted of racemic ephedrine hydrochloride (a dextrolevorotary ephedrine preparation), 0.5 Gm, homatropine hydrobromide, 0.03 Gm, and distilled water, 100 Gm. The advantage given was that the dilatation was obtained in fifteen to twenty minutes and persisted for a few hours. The preparation used in this examination was made up with buffer solution of  $p_H$  7.2 as a vehicle, in place of distilled water.

Then patients were tested with this combination (table). The eyes pained somewhat, and there was redness of varying degrees after instillation of the drops. Unfortunately, all but 1 patient had brown irises and required from 2 to 4 drops of the mydriatic to obtain effect. With the increasing number of drops the pain did not lessen. No patient obtained full dilatation. In this small group there were 4 patients who could get no more than a 6 mm dilatation. The ages ranged from 7 to 65 years. Three patients took from one hundred to one hundred and thirty-eight minutes to obtain a dilatation of only 6 mm. Most pupils reacted to light, and many could read 37 M type.

It was felt that by using ephedrine with homatropine or racéphedrine with eucatropine, the preparation might be less irritating. The burning was somewhat less, and a study of more cases could be attempted.

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<sup>37</sup> Hartlieb, R. Deutsche med. Wchnschr. 58 735, 1933, abstracted, Arch. Ophth. 10 134 (July) 1933.

*Ephedrine Hydrochloride and Homatropine Hydrobromide*—A solution of ephedrine and homatropine was used with 41 patients. The solution gave a burning sensation, but to a lesser degree than the racéphedrine-homatropine solution. In this group, there were 19 "blue-eyed" patients (table). All but 1 obtained full dilatation. Some pupils did not contract at all with 1 per cent pilocarpine hydrochloride. Thirty-four subjects obtained full dilatation of the pupil. The pupil contracted with 1 per cent pilocarpine hydrochloride sooner than when the racéphedrine-homatropine solution was used.

*Racéphedrine Hydrochloride and Eucatropine Hydrochloride*—This solution was the last preparation studied. There were 58 patients in this group. Of the 16 blue-eyed patients, 12 obtained maximum dilatation. It was possible to obtain full dilatation in 40 patients. In the majority the light reflex could be obtained (table), and almost a like number could read 37 M type at the height of dilatation. There were more or less burning, tearing and conjunctival injection, but less than with the other two mydriatics previously mentioned. Unlike these, pilocarpine contracted the pupil in the majority of cases and in less time.

#### CYCLOPLEGICS<sup>38</sup>

One of the purposes of this study was to determine how quickly the mydriatics studied could be neutralized by a mild miotic. A cycloplegic property in a mydriatic may prolong this period of neutralization. Possibly the drugs studied were better cycloplegics than was indicated by the results obtained, for the pupil dilated fully and so rapidly in some cases that cycloplegia did not have time to develop fully.

Dibutoline gave the greatest amount of ciliary paralysis, as determined by the Prince rule in conjunction with the correct refraction, to which was added a +3 D lens, with the patient looking through a 3 mm pupil at 37 M type.

The number of patients who gave evidence of some cycloplegic property in the mydriatic used were as follows:

Mydriatic	No. of Patients
Homatropine hydrochloride, 1%	23
"Syntropan," 6%	9
Atropine methylnitrate, 1%	17
Eucatropine hydrochloride, 1%	None
Eucatropine hydrochloride, 2%	4
Dibutoline sulfate, 5%	51
"Paredrine hydrobromide ophthalmic," 1%	12
"Paredrine hydrobromide," 3%	16
Phenylephedrine, 2.5%	9
Racéphedrine and homatropine	None
Ephedrine and homatropine	6
Racéphedrine and eucatropine	4

<sup>38</sup> Dr. Alfred Cowan assisted in evaluation of these data.



Of those drugs which could be neutralized by 1 per cent pilocarpine hydrochloride, dibutoline sulfate took the longest period for contraction of the pupil

#### SUMMARY AND CONCLUSION

In this study, twelve mydriatics were checked with regard to their ease of administration, rapidity of action and neutralization by a mild miotic—1 per cent pilocarpine hydrochloride

Ordinarily, these mydriatics worked more efficiently on cloudy or rainy days, and on patients with blue eyes. But there were exceptions. The same mydriatic on the same patient sometimes took a longer period for complete mydriasis when the patient was tested on different occasions. Some hazel-eyed or brown-eyed patients, as well as some older patients, took less time for mydriasis than "blue-eyed" and younger subjects.

The mydriatics in this study can be divided into drugs which are painful, and which include "syntropan," phenylephredine and the synergists racephedrine and ephedrine, in solutions of ephedrine and homatropine, racephedrine and homatropine and racephedrine and eucatropine, and drugs which are painless and easy to administer.

Homatropine hydrobromide, 1 per cent, atropine methylnitrate, 1 per cent, and dibutoline sulfate, 5 per cent, dilated the pupil in the greatest number of patients. Dibutoline sulfate, 5 per cent, gave definite cycloplegia in association with mydriasis in the greatest number of patients.

"Paredrine hydrobromide ophthalmic" (1 per cent) was less potent than dibutoline sulfate but was quite satisfactory as a mydriatic in a number of cases. Many of the patients with maximum dilatation after instillation of the "paredrine" had a pupillary reflex and could read 37 M type.

With "paredrine hydrobromide," 3 per cent, the mydriasis was more intense in that fewer drops were necessary and less time elapsed before mydriasis took place. A number of the patients given this solution could not read 37 M type during mydriasis, nor did they have a light reflex. However, the 3 per cent solution does not have much advantage over the 1 per cent solution of "paredrine hydrobromide" except in the few minutes gained for maximum mydriasis.

Eucatropine hydrobromide, 2 per cent, is the weakest of the non-painful mydriatics.

When 2 per cent eucatropine hydrochloride, "paredrine hydrobromide ophthalmic" (1 per cent) and 5 per cent dibutoline sulfate were used, their neutralization by 1 per cent pilocarpine hydrochloride with regard to the time interval took place in the order given. The longest period, that for dibutoline, was about four hours. Without miotics, these three mydriatics usually were neutralized spontaneously within twenty-four hours.

With respect to the suggestion of Peterson and Levinson<sup>39</sup> that the patient with glaucoma has a "lability of the cardiovascular-renal system," I had studied previously a larger number of patients with glaucoma. No consistently significant clinical or laboratory evidence was found which would be pathognomonic of glaucoma other than that which would be seen in similar patients of the same age, the diagnosis of "preglaucoma" would, therefore, be suggested by the presence of halos, a shallow anterior chamber and the pupillary reaction, rather than by laboratory studies.

Judging from the large number of older persons studied (of ages from 70 to 80 years) and the large number of drops of the mydriatic used in each case without ill effect, one may conclude that glaucoma is indeed a rare complication of mydriasis. Even in the case of "preglaucoma" in which a mydriatic has mistakenly been used, the rule of never discharging a patient until the pupil is contracted will obviate a disaster, particularly since much more powerful miotics than 1 per cent pilocarpine hydrochloride are available.

37 South Twentieth Street

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39 Peterson, W. F., and Levinson, S. A. Skin Reactions, Blood Chemistry and Physical Status of Normal Men and of Clinical Patients, *Arch. Path.* **9** 151 (Jan.) 1930.

## MALIGNANT RETROBULBAR NEURITIS

ADALBERT FUCHS, M D

SHANGHAI, CHINA

**I**N CHINA one often sees cases which are difficult to explain. Such a one was the case reported here.

CASE 1—On Sept. 25, 1945, Gen. C. H. H., aged 51, attended a Chinese dinner and drank wine like the other guests. The next morning he did not notice any change in his sight, but in the afternoon vision became impaired and in the evening he was unable to read. Sight in the two eyes was affected equally, everything was blurred, but he could recognize the door. Apparently, there was no central scotoma. On September 27, he was blind, and everything around him was black. He could see the window but not the intersections between the panes. Later, light perception was lost.

The wine was examined, but no toxic substance was found. The Wassermann reaction was negative, repeated Kahn tests gave negative reactions except once, when the reading was 1 plus, the spinal fluid was normal, the blood pressure was 106 systolic and 68 diastolic. Roentgenographic and general examinations failed to reveal any cause. As none of a great variety of treatments had any success, the patient went to the United States and was examined by several prominent ophthalmologists and neurologists. Air introduced into the spinal canal was of no assistance in detection of the cause of blindness. The diagnosis was atrophy of the optic nerve.

On March 27, 1947, I found the papilla of each eye white, the outlines distinct, the arteries narrow, the vessels without sheaths and the lamina cribrosa faintly visible. The pupils were equal and large, although they were sometimes small, they did not respond to light but reacted in convergence. There was complete amaurosis of each eye.

There was a widespread idea that the patient had been poisoned by the wine he drank during the dinner. But as the other guests at the dinner showed no symptoms, and the onset of blurred vision was not until twenty-four hours later, it is not likely that the atrophy of the optic nerve was due to intoxication. Methyl alcohol intoxication, especially, would have produced quite different symptoms and would have acted more quickly.

It is difficult to imagine what disease could have produced such sudden, complete blindness and, later, simple atrophy of both optic nerves, the American physicians who were consulted did not suggest any cause in their reports.

Two other cases which I have recently seen in China suggest an explanation of the sequence of pathologic changes, though they shed no light on the etiologic factors

CASE 2—A man aged 25 had onset of pain in the frontal region during the last days of February 1947. The left eye became blind on March 3 and the right eye on March 5. He received injections of neoarsphenamine and later underwent operation in a hospital for "glaucoma" of the right eye. There was no reason to think of an intoxication, as alcohol and medical drugs had not been taken. I saw the patient on March 22<sup>1</sup>. Both eyes were amaurotic, with both pupils very large and without reaction. The right eye presented a basal coloboma of the iris at 12 o'clock. Both eyes showed a normal fundus and normal tension. The Wassermann reaction was positive, the Kahn reaction, 4 plus. The spinal fluid was normal. The blood count was normal, a careful physical examination showed nothing remarkable. The sedimentation rate was normal, the coagulation time was 7 minutes. A roentgenogram showed a normal optic foramen and pansinusitis. The patient was treated with nicotinamide, typhoid vaccine,<sup>2</sup> vitamin B complex, a chiniofon (yatieu®)-casein preparation and penicillin (total dose, 2,400,000 units), given intravenously. On April 3, the middle turbinate bone was removed and a puncture of the sphenoid sinus was made, but no discharge was noted. Six days after his admission the disk became pale, and on April 10 both disks were atrophic and the patient was blind.

CASE 3<sup>3</sup>—A woman aged 39 became blind in the left eye in three days. She experienced slight pain when she moved the eye or when the eye was touched. When I saw her, the fundus was normal and no light reaction was present. Milk injections and two injections of typhoid vaccine did not produce a temperature higher than 37.5 C (99.5 F). After having tried diaphoresis, in vain, two intramuscular injections of 3 cc of a chiniofon-casein preparation was given. Vision did not return, and the patient left the hospital. Later, a colleague found atrophy of the optic nerve. The fundus of the right eye was normal, and all examinations to find the cause of blindness in the left eye were without results.

In case 2, the disease of the eye differed from that in case 1 only in that the condition did not start at exactly the same time in the two eyes. The right eye became blind two days after the left eye. Moreover, in case 2, the physicians were unable to get a clear picture of the developing pathologic process, and an operation was therefore performed for glaucoma.

Case 3 differed from the first 2 cases in that the blindness attacked only the left eye. The rapid deterioration in vision and the complete loss of the light reflex in a few days were similar in the 3 cases.

Without doubt, these 3 cases illustrate a special type of retrobulbar neuritis, which I shall call malignant retrobulbar neuritis. They were

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1 Dr L. U. Miao, of the Red Cross Hospital, Shanghai, supplied the history in case 2.

2 I was pleased to find fever treatment being used so much for retrobulbar neuritis, as I inaugurated this form of therapy for the disease.

3 Dr Nie, St. Marie Hospital, Shanghai, furnished the history in case 3.

characterized by sudden onset, by complete disappearance of vision and of the light reflex of the pupils and by resistance to all forms of treatment which are known from experience to be efficient even in refractory cases of retrobulbar neuritis

The fact that in all these cases the papilla was normal in the early stages of the disease shows that a poison or toxin could not have been the cause, otherwise, some signs in the central or retinal vessels, especially contraction of the arteries, would certainly have been noted

I have seen only a few cases of retrobulbar neuritis in which total blindness occurred. Further, in these cases the blindness was binocular, the onset was sudden and light perception disappeared. These ocular symptoms formed part of an encephalomyelitis optica, and the papillae showed prominent edema. In these cases there were several symptoms of general nervous disease, such as paraplegia of the lower extremities, or palsy of the abducens nerve, nystagmus and sudden appearance of the Babinski reflex, in 1 case. The choked disk in these cases of encephalomyelitis was apparently due to location of the focus in the optic nerve close to the lamina cribrosa, so that the associated edema produced swelling of the papilla, with no hemorrhages or white foci of fatty degeneration in the fiber layer.

The aforementioned cases of encephalomyelitis differed from the Chinese cases of malignant retrobulbar neuritis described here in that vision came back to a certain extent after adequate treatment. The accompanying neurologic symptoms in the former cases make the participation of the optic nerve easily understandable. In the cases of malignant retrobulbar neuritis, competent neurologists were unable to find any neurologic symptoms (case 1), demonstrating that in the latter disease a quite different etiologic factor was involved.

This type of malignant retrobulbar neuritis seems to be rare, and I have found no similar case in the literature, only in his comprehensive paper on retrobulbar neuritis did Werner<sup>4</sup> mention the cases of 2 very old patients who became almost totally blind, but both his cases differ from the present ones in the presence of papillitis.

I saw the 3 cases reported here within a few months, and I have the impression that malignant retrobulbar neuritis is not rare in China. However, Dr. Eugene Chen, professor of ophthalmology in West China Union University, Chengtu, Szechuan, told me that he had not seen a case in his practice.

It may be of interest here to give the history of a case of retrobulbar neuritis the symptoms of which resembled those in a severe case seen

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4 Werner, L. E. *Tr. Ophth. Soc. U. Kingdom* 45: 376, 1945

in Austria but in which the resistance to energetic treatment was much greater than I have ever encountered

CASE 4—A nurse aged 20, at 7 a m on Jan 20, 1947, suddenly began to see everything red in the temporal half of the visual field. Examination four hours later revealed visual acuity of 6/75 in the right eye and 6/6 in the left eye, the papillae were normal. The next day vision had dropped to perception of hand movements at 30 cm and light sensation at 3 meters, with light projection present only on the temporal side. Tension was normal. Roentgenographic examination of the nasal sinuses and physical examination revealed nothing abnormal. Six days after the onset of symptoms, the patient was given 10 cc of milk intramuscularly and the same amount on the following day. On the next day she had high fever, and light projection was restored in every direction. Typhoid vaccine was injected intravenously on February 14, 17, 21 and 24, and vision gradually improved to ability to count fingers at 25 meters. The visual field apparently was concentrically constricted. On February 28, and on March 4, 8, 15 and 18, typhoid vaccine was again injected. Vision rose to 6/15, and on April 18, after two fever treatments, vision was 6/12 and she read Jaeger test type 4 at 18 cm.

When I saw her, the patient had normal vision in both eyes, and her physician had concluded that she had had hysterical amblyopia. Pupillary reaction was good, and I was informed that it had always been present. The papillae appeared normal on both sides and were of normal color. There was no tenderness of the eye on movement or touch, although for the first three days after onset she had had a slight sensation on the right temple and above the eye during movement.

As essential proof that this case was one of retrobulbar neuritis, with the right eye she saw a red mark 2 cm in diameter as less red, and as grayer, than with the left eye. Examination of the visual field showed that she did not see red and blue at all when marks 1 cm in diameter were used. Larger marks were seen as grayer at the periphery than in the center. Small white marks she saw only in an area 8 to 10 cm at a distance of 35 cm.

It appears that no central scotoma was present, but only a concentrically contracted field. The changes in the value of colors show that in this case there was no hysteria. Apparently, the disturbance was an atypical retrobulbar neuritis with a particularly high resistance to treatment, as many inductions of fever were required for cure and recovery was prolonged. I saw the patient again much later, and there was no change in the color of the disk.<sup>5</sup>

Case 4 forms a transitional type between the malignant and the ordinary type of retrobulbar neuritis. The patient did not at any time lose the light reflex and therefore was never so seriously ill as are patients with the malignant form. It is amazing that she recovered such good vision and that no pallor of the papilla remained. The case

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<sup>5</sup> Dr Lewis W S Chang, of the Central Hospital, Nanking, furnished me with the history in case 4.

is in particular contrast to cases of multiple sclerosis, in which one may hear nothing of visual disturbance and yet extreme temporal pallor of the disk appears insidiously

#### SUMMARY

In 3 cases loss of vision and the light reflex, binocular in 2, developed in two or three days, while the fundi remained normal. Later, primary atrophy of the papilla occurred, and, in spite of energetic treatment, there was not the slightest restoration of vision. For these reasons, I have called this condition "malignant retrobulbar neuritis."

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# TECHNIC OF GONIOTOMY FOR CONGENITAL GLAUCOMA

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**G**ONIOTOMY is an operation for stripping or peeling embryonic tissue from the wall of the angle. If the cornea is clear, the operation is performed under direct vision with the aid of a prismatic contact glass specially devised for this purpose. If cloudiness of the cornea prevents the use of the glass, the operation is performed without it.<sup>1</sup>

In recent articles<sup>2</sup> observations on congenital glaucoma and the results obtained during the past ten years with goniotomy performed on 76 eyes presenting congenital glaucoma were published. In 66 of these eyes pressure was normalized and vision was maintained or restored. In 10 eyes the operation was unsuccessful. It is the purpose of the present article to describe the technic of goniotomy, its mode of action and its indications and contraindications. The importance of early diagnosis and prompt operation is stressed. The operation is exacting. It demands teamwork and meticulous attention to detail of technic in order that a high incidence of good results may be obtained and hemorrhage, which may have serious consequences, avoided. Experience with gonioscopy and acquaintance with the variable picture of congenital glaucoma are helpful.

## MODE OF ACTION OF GONIOTOMY

In congenital glaucoma the angle presents a characteristic gonioscopic appearance, which shows little individual variation. In 75 of 76 eyes the characteristic condition appeared to consist in an abnormal insertion of the iris by means of adventitious mesoblastic tissue into the wall of the angle anterior to its site of normal insertion. Gonioscopic examination with a hand slit lamp and corneal microscope held in the hand reveals that the iris continues in a horizontal plane until it reaches

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Read at the Fifty-Second Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, Oct 16, 1947

1 The approach to the angle across the anterior chamber was first introduced by de Vincentitis in 1892, and some successes were reported. The method later fell into disuse.

2 Barkan, O. Operation for Congenital Glaucoma, *Am J Ophth* **25** 552-568 (May) 1942, Goniotomy for Congenital Glaucoma, *ibid* **33** 526-533 (Feb) 1947



the posterior surface of the cornea. This is in contrast with a backward dipping of the iris seen in the normal eye, which forms a sinus, or the so-called angle of the anterior chamber. The point of attachment corresponds to the position of the anterior border ring of Schwalbe. The area of transition from the anterior surface of the iris to the posterior surface of the cornea is covered by a gelatinous-looking, semitransparent substance. This area may be so narrow that it barely constitutes a line. It may be wider, in which case the beam of light shows the tissue to be in a plane anterior or axial to the true angle wall, the presence of which can in some cases be discerned in a deeper plane. Delicate arborescences of uveal meshwork which cross the angle can be seen resting on the semitransparent substance which fills the angle behind them. From this finding, and from the flare of the beam of the

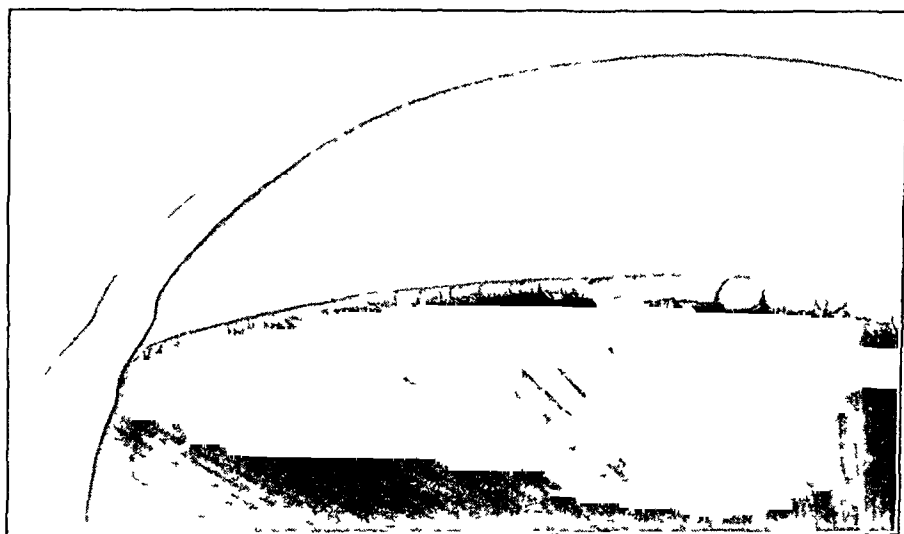


Fig 1—Postoperative microgonioscopic appearance at the point of transition between the area on the right, in which the angle has been stripped, and the neighboring, untouched, region

slit lamp traversing it, it is evident that the angle is not an optically empty space. This becomes especially evident after operation at the point of transition between the area in which the angle has been stripped and the neighboring, untouched, region (fig 1). The gonioscopic appearance corresponds to that which would be expected from a study of histologic sections of eyes with congenital glaucoma enucleated in the early stages. Gonioscopic study of normal eyes of infants indicates that the chamber angle does not assume an adult appearance until after the age of several months, indicating that the uveal meshwork continues to regress after birth. This appearance can in most cases be distinguished from the pathologic persistence of uveal tissue which is present in congenital glaucoma. Postoperative gonioscopic exami-

nation in the successful cases revealed that the procedure had been effective in stripping from one fourth to one third of the circumference of the filtration angle the persistent embryonic tissue that obstructed it. Figure 1 shows a case in which stripping had resulted in normalization of pressure for nine years, to date. Analysis of the present series of cases suggests that stripping of this amount of the angle is sufficient and is the *sine quo non* of successful normalization of pressure. It also suggests that stripping of only a part of the circumference is adequate to permit the pressure-regulating mechanism to assert itself and permanently to maintain normal tension and function. Since this effect has been observed in individual cases as long as ten years after goniotomy, and since recurrence of increased pressure has been the exception, it appears that the stripped angle does not again become blocked and that the effect is permanent.

In all cases of bilateral glaucoma in this series, and in most cases of the monocular condition, judging from results obtained by stripping the angle and from a comparison of preoperative and postoperative gonioscopic findings, the initial increased pressure appeared to be the result of obstruction of the angle due to arrested regression of the uveal meshwork. Since removal of the persistent embryonic tissue resulted in normalization of pressure, it must be assumed that Schlemm's canal was present. There was no sign that either internal cyclodialysis or external filtration had taken place in any of these cases. It may be concluded, therefore, that the mode of action of goniotomy consists in restoring access of aqueous to Schlemm's canal by removal of obstructing tissue.

In 1 case there was direct gonioscopic evidence of the presence of Schlemm's canal in that portion of the angle from which the obstructing tissue had been removed. This evidence consisted of a pink band lying external to the trabeculum in the position of Schlemm's canal. In the adult this pink band has been shown by Kronfeld<sup>3</sup> to be produced by blood in Schlemm's canal. The presence of Schlemm's canal is suggested by postoperative gonioscopic observations in the aforementioned successful cases. It is confirmed by the analysis of anatomic examinations of 84 specimens taken from eyes on which no operation had been performed, as reported by Anderson<sup>4</sup>. He found that Schlemm's canal was present in 75 per cent of the earliest specimens. No sign of it was found in more than one-half the specimens taken from children over 2½ years of age. He suggests that the canal becomes closed in the later stages as the result of distention of the eyeball and of increased intraocular

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3 Kronfeld P. C., and others. Gonioscopic Studies on the Canal of Schlemm, *Am J Ophth* 25 1163-1170 (Oct) 1942

4 Anderson, J. *Hydrophthalmia or Congenital Glaucoma*, London, Cambridge University Press, 1939, p 151

pressure The evidence obtained from these specimens confirms the effectiveness, as judged by gonioscopic examination, of stripping the angle in early congenital glaucoma

#### URGENT NEED OF EARLY OPERATION

The mode of action of goniotomy, as explained in the foregoing section, shows the importance of early diagnosis for a successful outcome of operation and explains why the chances of establishing outflow by this procedure may be expected to diminish with the duration of the condition It is essential to operate early, before prolonged distention of the eyeball has caused obliteration of Schlemm's canal Other important reasons for early diagnosis and prompt operation are (1) restoration of vision by means of clearing the cornea corneal cloudiness being largely reversible in the early stages and becoming progressively less so with the later stages, (2) prevention of amblyopia due to prolonged obstruction of vision by cloudiness of the cornea, (3) prevention of development of permanent scar formation from corneal cloudiness, (4) prevention of injury to the optic nerve caused by prolonged pressure

In general, it is important to prevent progressive enlargement of the eyeball before distention has produced permanent changes and to encourage development of normal anatomic relations and of physiologic function during the period of growth

The symptoms of increased intraocular pressure in congenital glaucoma may be present at birth, or their onset may be rapid or sudden during the first few months of infancy In most cases symptoms are cloudy cornea, photophobia and other signs of irritation and congestion In the rare cases of slow onset there are no congestive symptoms Pressure should be measured with the tonometer with the patient under ether anesthesia, which must be deep enough to insure complete relaxation at the moment of measurement in order that the recording of false values may be avoided The appearance of congestive symptoms is prone to lead to a faulty diagnosis of blepharitis, conjunctivitis or keratitis, causing loss of valuable time and bearing tragic consequences

The initial cloudiness of the cornea is associated with roughening of the corneal epithelium This disturbance of the cornea is the chief cause of the irritative symptoms and photophobia, which are further aggravated by exposure to air and light If the corneal cloudiness is allowed to persist, it is superseded by permanent scarring with associated irregular astigmatism and ensuing amblyopia of greater or less degree

Glaucomatous atrophy of the optic nerve was the exception in the present series of infants and children It occurred only in the few cases in which normalization of pressure was unduly delayed In infants it is not nearly so urgent to protect the optic nerve head from pressure as it is to relieve cloudiness of the cornea

If soon after its inception increased intraocular pressure is normalized by goniotomy, transparency of the cornea is almost completely restored and maintained, and vision is afforded the opportunity to develop. When this is borne in mind, the urgency of prompt relief of increased pressure is evident.

### RESULTS

The results of goniotomy<sup>5</sup> in cases of congenital glaucoma are summarized in the following tabulation:

Number of infants and children	51
Eyes on which goniotomy was performed	76
Eyes successfully treated by goniotomy (pressure normalized, vision maintained or restored)	66
Eyes unsuccessfully treated with goniotomy	10
Eyes to which goniotomy was not applicable	11

It has been my custom to prescribe the use of miotics three times a day for two months after operation. The result of the operation was considered successful when intraocular pressure did not rise higher than 35 mm of mercury with the McLean tonometer or 21 mm with the Schiøtz tonometer three months after operation, no miotics having been used during the two weeks preceding measurement of the pressure.

In the successful cases the time which had elapsed since the date of operation varied from six months to ten years. There were recurrences in 2 eyes, mentioned in the next paragraph. The oldest patient (2 eyes) was operated on ten years ago, 5 eyes were operated on seven years ago, 8 eyes, six years ago, 21 eyes, from four to six years ago, 11 eyes, from two to four years ago, 9 eyes, from one to two years ago, and 10 eyes, from three to twelve months ago.

The recurrence of increased pressure which took place in 2 eyes was relieved by a second goniotomy in both instances. In 1 patient, pressure increased in the left eye eight years after operation. In another, pressure increased in the left eye four years after operation. Gonioscopic examination showed that the stripping of the angle had been insufficient.

Repeated operations were necessary in 22 eyes before pressure was permanently normalized. One operation sufficed for each of 45 eyes. In some cases goniotomy was performed four times on each eye before permanent normalization was attained. The ultimate result was excel-

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<sup>5</sup> Goniotomy in infants and the procedure in adults are two distinct operations, which differ in rationale, technic and effectiveness. In infants, the operation, which has been developed to a relatively satisfactory conclusion, consists in removal of occluding fetal meshwork from the angle. In adults, in whom it has not yet shown a degree of consistent efficacy adequate to recommend its employment except in the occasional case, the objective is to incise the wall of the angle, that is, the trabeculum proper. For this reason, it is suggested that the term goniotomy be applied only to the operation performed on infants, and goniotrabeculotomy, or trabeculotomy, to the procedure carried out on adults.

lent I believe it is better to err on the side of conservatism, and partially strip the angle with safety on repeated occasions, than to attempt to do an extensive stripping at one operation, at the cost of greater hazard. Cases in which repeated operations were required before permanent normalization was attained are not listed as cases of recurrence.

The operation was performed with the eye under the contact glass on 20 eyes. In all these eyes the goniotomy was successful. Repeated operation is the exception when one operates under the contact glass. In 56 eyes the operation was performed without the contact glass because of corneal cloudiness. On 18 of these eyes repeated operation was necessary. In 8 eyes which had been ineffectively trephined, goniotomy normalized tension.

#### ADVANTAGES, DISADVANTAGES AND HAZARDS

Striking among the results of goniotomy are absence of cosmetic disfigurement and preservation of a round, central, freely reacting pupil.

A disadvantageous feature of the operation without the glass is the need of repeating the operation in one third of the cases in order that permanent normalization of tension may be obtained. Moreover, a consistently successful performance is associated only with a considerable degree of experience and highly trained assistance.

A hazard of the operation is excessive hemorrhage or iridodialysis if the root of the iris is incised. Vision was lost in 2 eyes early in this series as the result of excessive hemorrhage. Recently 1 eye, in a late, neglected case of a 2½ year old child, was lost as the result of a massive intraocular hemorrhage, which occurred on the sixth postoperative day. As in any other intraocular operation, infection is a possible complication, but it was not encountered in this series. A severe reaction, which could be considered an infective uveitis, occurred in 1 case. As always, the operation had been performed on different days, in this instance after an interval of three weeks. The condition cleared after eighteen days, leaving in one eye a small central opacity of the anterior capsule, in the other an anterior adhesion produced eccentricity of the pupil. Tension was normalized, and it is evident that useful vision is developing. In no case has sympathetic ophthalmia yet occurred.

#### INDICATIONS AND CONTRAINDICATIONS

Goniotomy is indicated in all cases of congenital glaucoma in which increased pressure is the result of obstruction of the angle by persistent embryonic tissue, provided that Schlemm's canal has not been obliterated by, and degenerative changes have not resulted from, prolonged distention of the bulbus. This criterion includes the majority of cases of congenital glaucoma in the early stages. It also includes those cases in which the condition has run a noncongestive course over a long period.

and in which the cornea remains clear, the optic nerve undergoes little damage and the bulbus is only moderately enlarged. Good central vision is maintained in these cases. Since the cornea is clear, goniotomy can be performed under direct vision with the aid of the glass, and may be effective even several years after the onset of symptoms. Excellent results were obtained in some of these patients at 4 and 6 years of age, with corneal diameters of 14 mm. However, in general, the sooner the procedure is applied after onset of symptoms, the more effective is the operation in maintaining or restoring vision. Results may be dramatic when the bulbus is in the early congestive phase, associated with cloudiness of the cornea. In such cases the urgent need of early diagnosis and prompt adequate operation can hardly be overemphasized.

Goniotomy is contraindicated in older children whose eyes are in an advanced stage of glaucoma and, as a result of prolonged congestion, show corneal scarring, cloudiness and a corneal diameter of 15 mm or more. In these enlarged, "buphthalmic" eyes, the danger of hemorrhage is increased because of dilated vessels and establishment of a collateral circulation. Hemorrhage is absorbed more slowly, no doubt owing to the degenerative condition of the eyes and to their altered circulation. Schlemm's canal may be obliterated as a result of the distention.

When permanent obliteration of the canal has taken place, or when repeated goniotomies have proved ineffective, iridencleisis or cyclodiatomy may be tried.

In some rare cases of unilateral congenital glaucoma the condition appears to be the result of other anomalies, such as an aberrant reflection of the stroma of the iris to an insertion at the anterior border ring. The extremely rare cases of narrow angle (iris block) glaucoma<sup>6</sup> in small children do not come within the scope of this article, since goniotomy is not applicable to them.

#### TECHNIC OF GONIOTOMY

There are two major procedures of goniotomy. If the cornea is clear, goniotomy is performed by direct vision under a prismatic contact glass, if the cornea is cloudy, the operation is done without the glass. The general considerations which the procedures have in common will be treated first.

#### GENERAL CONSIDERATIONS

*Preoperative Measures*—Pediatric examination, including roentgenologic study of the chest for enlarged thymus, is performed in all cases. In the case of infants, the usual diet is maintained up to six hours

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<sup>6</sup> Barkan, O. Glaucoma. Classification, Causes, and Surgical Control, *Am J Ophth* **21** (Oct) 1938, An Operative Procedure for Glaucoma of Shallow Chamber Type, *Arch Ophth* **21**:331-345 (Feb) 1939.

before operation, solution of dextrose is forced up to four hours before operation to avoid dehydration with associated hyperpyrexia. In order that surgical treatment may not be delayed, and since ether may have to be given several times in the course of the following weeks, every effort should be made to prevent the infant from catching cold. Instillations of miotics, preferably neostigmine methylsulfate, 5 per cent, are continued, usually every three hours, while the patient is awake until one and one-half hours before the time of operation. An extra drop is instilled three times at intervals of one-half hour before operation in the eye to be operated on. If circumstances permit, 1 drop of "sulmefrin" (sodium sulfathiazole sesquihydrate plus *dl*-desoxyephedrine) is instilled three times a day for several days before operation.

*Anesthesia*—In view of the delicacy of the operation as applied to infants, who may be only a few days or weeks old, and who may show other congenital defects, anesthesia is an important consideration. A preliminary injection of atropine is given forty-five minutes before operation. Ether is administered through a small airway (intraparyngeal insufflation). A generous supply of oxygen should be assured at all times. While the patient is being prepared the lids must be kept closed with moist pledgets, but without pressure, since the cornea in congenital glaucoma is extremely susceptible to exposure and to pressure. For the same reason, the heat generated by operating room lamps should be avoided. Anesthesia must be sufficient at the moment of operation to prevent movement of the patient. In children over 6 months of age a small dose of paraldehyde is administered forty-five minutes before operation. Postoperative agitation, which may follow ether anesthesia, is not harmful, since there is only a small, obliquely placed puncture wound, which does not permit egress of ocular contents. Before the patient is draped, the intraocular pressure is taken with a tonometer, the base of which has been sterilized. The corneal diameters are measured, and the condition of the cornea and the size of the pupils are noted. Sometimes the decision as to which eye to operate on can be made only at this time.<sup>7</sup> Then the positions of the patient, operator, assistant, anesthetist and instrument table are arranged accordingly.

*Position of Patient*—The infant is placed on a circumcision board for the right eye, on the center of the operating table, for the left eye, with the head end of the board protruding obliquely from the table. For goniotomy under the glass the eye should be 47 inches (120 cm) above the floor in order to permit a convenient position for an operator 5 feet 10 inches (178 cm) in height. For goniotomy without the glass

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<sup>7</sup> In cases in which the decision has already been made, the taking of the tension is dispensed with as a preliminary procedure, in order to reduce the time of anesthesia.

the patient's eye should be 46 inches (117 cm) or less above the floor in order that the operator may look vertically down on it. A pillow or towel is placed under the head, bringing it into a horizontal plane. The anesthetist maintains the head in position during the operation.

*Position of Operator and His Assistants*—The operator stands on the side of the eye to be operated on: for the right eye, at 11 o'clock, for the left eye, at 4 o'clock. The illuminator, holding a hammer lamp, must be high enough, standing on a platform if necessary, to obtain a good view of the field of operation. He stands on the same side as, and to the right of, the surgeon for the operation with the glass, on the opposite side for operation without the glass. The assistant fixates the bulbous with two Gifford forceps with lock, standing at 3 o'clock for the right eye and behind the head for the left eye. The anesthetist is on the side opposite the operator, for the right eye at 5 o'clock, in order not to interfere with the assistant, who is standing at 3 o'clock.

*Magnification*—The operator uses a 2.50 D sphere hanger over his correction. He wears a binocular head loupe 5.00 D sphere (Hess head loupe), which he uses in case the anterior chamber is deepened through a corneal puncture made with a discission knife and for goniotomy without the glass. He does not use it for goniotomy with the glass.

*Illumination*—The room is in semidarkness. One lamp, situated at some distance from the table and directed away from it, is in readiness for general utility purposes. The field of operation is illuminated by a hammer lamp,<sup>8</sup> which is made of light plastic and is air cooled. It is used in both procedures, but manipulation differs respectively. The illuminator must be familiar with and trained in the procedure. The technique of illumination is especially important in goniotomy by direct vision under the glass and must be carefully rehearsed before the operation.

*Instrument Table*—The instrument table is on the side of the eye to be operated on (fig. 2).

*Preparation of Patient*—Lashes are clipped (with Stevens scissors and ointment, which is wiped off with cotton spindle after each clip). The face is prepared and the eye irrigated in the usual manner. After the patient is draped, a face mask is applied, this should be of moistened gauze, in order to be easily molded to the region.

#### GONIOTOMY UNDER THE CONTACT GLASS

Once the glass has been applied, time is the essence of goniotomy. A complete check, therefore, is made beforehand in order to insure that everything is in readiness and in position on the instrument table. The

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<sup>8</sup> This lamp was demonstrated before the Section on Ophthalmology at the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 4, 1946. A description of it is in publication.



speculum is passed through two holes made in a piece of rubber dam 6 inches (15 cm) square. The height of the assistant and that of the illuminator are checked. Either or both of these persons may require a platform to stand on. The lids are kept closed throughout the preparation. A few minims of epinephrine hydrochloride (1:1,000) is injected into the outer canthus with a no. 30 needle and a 1.5 cc Luer syringe, after one minute a canthotomy is performed with straight Mayo scissors. The quartz surgical contact glass, which has been cold sterilized, is dried and placed on gauze in a small bowl on the instrument table. The knives (two goniotomy and two discission knives) are now placed on the table, with points toward the operator.

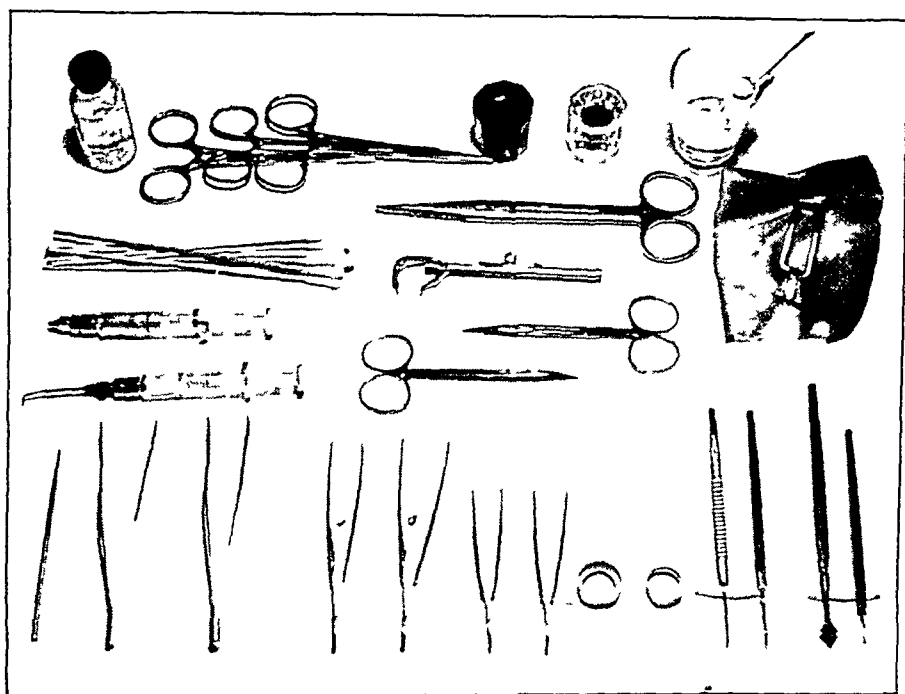


Fig 2—Usual setup of tray for goniotomy, with ampule of isotonic solution of sodium chloride, mosquito hemostats, Dappen glass, containing tincture of iodine, Dappen glass containing solution of fluorescein sodium, 1 per cent, medicine glass containing isotonic solution of sodium chloride and glass rod, speculum with rubber dam, applicators, Mayo scissors, Luer-Lok syringe, 2 cc with no. 30 needle, containing isotonic solution of sodium chloride, caliper, Stevens scissors, lacrimal dilator, splinter forceps, Gifford forceps with lock, Bishop Harman forceps, surgical contact glass (small and large), goniotomy knives, keratome, discission knife, narrow

The operator stands at 11 o'clock for the right eye and at 4 o'clock for the left eye. The platform on which the illuminator is about to stand is already in position to the operator's right. The instrument table and the surgical nurse are also to the right of the operator. The speculum is now inserted and the rubber dam trimmed, especially on the nasal side. On the temporal side the dam covers the lids, preventing contact

of the knife with them and relieving the operator's mind of this important detail. The cornea is moistened when necessary with isotonic sodium chloride solution U S P applied by means of a glass rod. The eye is fixated by the assistant 3 to 4 mm posterior to the corneoscleral border at 12 and 6 o'clock, or at the insertions of the vertical muscles, by means of two Gifford forceps with spring lock. He must be mindful not to touch the lock, lest it spring open during the operation. The head and eye are rotated away from the surgeon, who applies the contact glass in the usual manner by injecting isotonic sodium chloride solution between it and the cornea through a curved gold cannula and 1.5 cc Luer syringe.

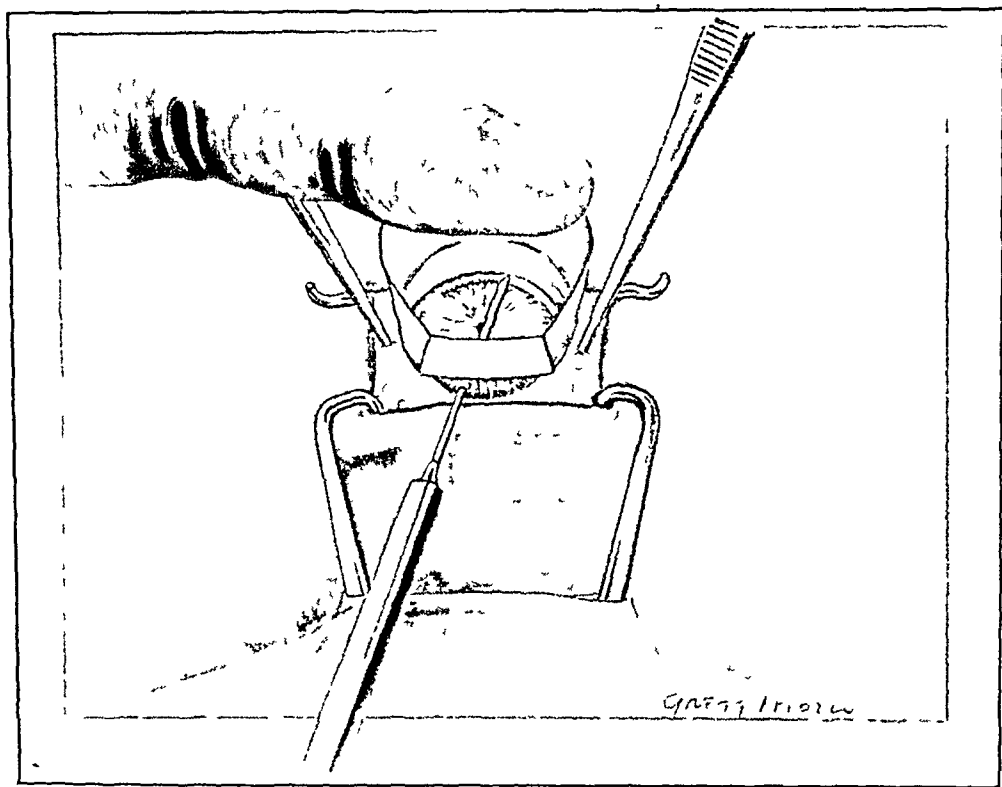


Fig 3—Goniotomy, or stripping of the angle under the glass. The root of the iris retracts behind the blade, leaving a white wake behind it, which is the wall of the angle.

When the surgeon is operating on the right eye (fig 3), the fixator's right hand holds the forceps at 12 o'clock and the left at 6 o'clock. The left hand must be in such a position that it does not obstruct the view of the illuminator as he moves counterclockwise. When the surgeon is operating on the left eye, his right hand is at 6 o'clock and his left at 12 o'clock. Regardless of the side under operation, the fixator, unless tall, should stand on a platform in order to insure visibility of the eye throughout the procedure and to prevent the tendency, arising from poor visibility, to retract or dimple with the forceps. The surgeon supports

the glass with the index finger of his left hand. Two indentations on the glass prevent the finger from slipping. The latter abducts the eye slightly in order to expose a strip of the temporal portion of the cornea 2 or 3 mm wide, where the puncture is about to be made. With abduction, the eye can be made to offer resistance to the glass when this is pressed more firmly against it by the operator's finger at the moment of puncture, thus preventing ingress of air at this critical moment. The operator applies the end of a cotton applicator previously dipped in tincture of iodine U S P at the intended site of puncture. The goniotomy knife is then passed to him by the instrument nurse. She withdraws the instrument table, and the illuminator assumes his position on the platform immediately to the operator's right.

The illuminator stands on the platform sufficiently far removed from the surgeon to provide room for him to sway counterclockwise during the progress of the incision. The illuminator must stand with feet well apart in order to be able to sway in unison with the counterclockwise movement of the surgeon without having to take a step. He maintains the lamp in contact with the temple of the surgeon, at the same time looking down the top of the shaft of the lamp, so that he may have the same view of the angle and of the blade of the knife as the surgeon. The heads should maintain contact. Perfect synchronization of heads and light is necessary, they must move as one unit. A light on a head band did not give as good results as the technic described.

The eye first having been rotated two hours counterclockwise, puncture is made in the right eye at 10 o'clock, and in the left eye at 4 o'clock, 1 mm anterior to or axial with the corneoscleral border and oblique, so that the corneal wound is valvelike, or trapdoor-like. At the moment of puncture, extra pressure is exerted by the operator's index finger on the glass in order to prevent ingress of air. Pressure must be exerted in the direction of the optic axis, as tilting of the glass permits entrance of air. For the same reason, dimpling of the sclera with the fixator's forceps must be avoided. The operator guides the knife across the pupil to the opposite side. In traversing the chamber, the knife must always cross the optic axis. When the knife crosses the optic axis, the diameter of the arc described after the opposite angle is engaged will be greater than the diameter of the circumference of the limbus. Therefore, the point of the knife remains engaged. When the knife does not cross the optic axis, the contrary holds true. When an arc smaller than that of the limbus is described the point of the knife becomes disengaged and too small an incision is made. Moreover, the extra movement of advancing the knife necessary to maintain contact with the wall of the angle is likely to result in picking up iris tissue near the root, with consequent iridodialysis and hemorrhage. The blade is inserted just anterior to the root of the iris and is moved counterclockwise in this plane as long as

visibility permits. This usually amounts to several millimeters, or from one-fourth to one-third the circumference. During this excursion of the blade, the shaft is rotated around its axis in a clockwise direction to encourage a stripping action and to prevent the blade from moving posteriorly out of the intended plane into the dangerous region of the ciliary body. During stripping under the glass, the root of the iris is seen to retract behind the blade, leaving a white wake behind it, which is the wall of the angle (fig. 3). In some cases this has the appearance of a cut piece of parchment paper that drops backward as the incision proceeds. Stripping should be done under complete control and the blade placed immediately above the root of the iris, care being exercised to avoid blood vessels at that site, which in some cases are clearly visible. There may be a slight sensation of grating as the blade proceeds, the fixator may recognize the need of exerting slight resistance. Since picking up the root of the iris causes hemorrhage, it is advisable to start well anterior to the root and to strip or peel off the insertion of the iris from above. When stripping has been completed, the knife is quickly removed, without loss of aqueous in most cases, care being taken to avoid enlarging the puncture wound in the cornea by slight pressure against the back of the blade during its removal. The contact glass and fixating forceps are withdrawn. After a few seconds, a slight oozing of blood of venous color appears in the anterior chamber along the line of stripping, this is absorbed within a few hours. If, after removal of the knife, the pupil should be eccentric, the cornea is tapped near the puncture with a spatula, or the tip of a lacrimal dilator is inserted to prevent adhesion of iris to the inner lip of the wound.

The speculum is removed and the canthotomy closed with surgical gut. Physostigmine ointment, 1 per cent, and sulfathiazole ointment, 10 per cent, are inserted into the conjunctival sac. Binocular pads are applied, the one over the treated eye being covered with a metal shield. The child is placed in bed on the side of operation in order that any blood may settle on the opposite side of the chamber. Arm cuffs are applied. With older children, restrainers may be necessary. Elixir of phenobarbital, 1 drachm (3.7 cc), may be indicated. In cases of bilateral glaucoma it has been customary after twenty-four hours to instil neostigmine methylsulfate, 5 per cent, in the intact eye and, after forty-eight hours, in the eye operated on, thereafter instillation of drops is continued three times a day in both eyes. Only one eye is operated on at a time.

If the different steps of the procedure have been reviewed before operation, there should be no loss of time at operation, so that once the glass is applied goniotomy is quickly completed.

If goniotomy under the glass is not feasible, the operation is performed without the glass. Operation performed under the contact glass is desirable whenever possible. In the past, various procedures, such

as use of glycerin or hypertonic solution of sodium chloride or retrobulbar injection of epinephrine (1 1,000), have been tried with a view to clearing a cornea which has become cloudy during preoperative maneuvers and application of forceps and the glass without success. Release of a small amount of aqueous through a valvelike corneal puncture made with a Graefe knife was also tried. It cleared the cornea but did not permit of adequate operation under the glass because of complicating circumstances. Recently, a preliminary operative abrasion of a sector of the epithelium prior to application of the contact glass has enabled operation under the glass in cases in which it has heretofore been impossible.

#### GONIOTOMY WITHOUT THE CONTACT GLASS

The preparatory measures already outlined for goniotomy under the glass are carried out. The precautions mentioned under "General Considerations" are observed. The height of the eye should be such that the operator looks vertically down on it. Illumination is provided by the hammer lamp carried on the end of a rod so that the light falls as nearly vertically from above as possible. The illuminator stands opposite the surgeon, for the right eye at 4 o'clock and for the left eye at 10 o'clock. The rubber dam on the nasal side must be trimmed well back to avoid its casting a shadow on the field of operation. The bulb is fixated with two forceps held by the assistant, in the same manner as for the operation under the glass. The forceps should be placed vertical to the sclera and must include episcleral fibers in order to permit of resistance or counterpressure on the part of the fixator during stripping. The surgeon applies Bishop Harman forceps at the contralateral limbus, helping to fixate and guide the rotation from there. If the assistant is not sufficiently experienced with this operation, it is best to divide the fixation between him and the surgeon. In this case the surgeon fixates with the Gifford forceps with lock in his left hand at 12 o'clock on the right eye and at 6 o'clock on the left eye, while the assistant fixates with his left hand at 6 o'clock on the right eye and at 12 o'clock on the left eye.

Canthotomy is indicated in most cases. In small infants, in whom the operation is especially delicate, the head is rotated toward the surgeon and the eye slightly abducted in order to bring the nasal limbus into a frontal plane with the surgeon's line of regard. In the case of a greatly enlarged eye this lateral movement is limited because the temporal limbus disappears as the result of even slight abduction.

The puncture in the cornea is made as already described, care being taken that it is oblique (valvelike) in order to encourage retention and reformation of the anterior chamber. It is made on the right eye at 10 o'clock, the eye having first been rotated counterclockwise the equivalent of 2 hours. The blade of the knife crosses the pupil and disappears behind the limbus on the opposite side in a plane just anterior to that of the

iris As it engages the angle wall and starts its excursion in a counter-clockwise direction, slight resistance is felt Its tip can be seen through the sclera from the outside Seen through the cornea, the knife appears 0.5 mm farther anterior than it is in actuality This appearance must not influence the surgeon to guide his knife farther posteriorly A posterior position of the blade is the greatest hazard of the operation It is better to err on the conservative side by maintaining a more anterior plane, at the risk of not stripping the angle The operation can always be repeated Rotation of the knife clockwise around its own axis helps to prevent it from being guided or from slipping to a posterior position Stripping the angle wall is usually associated with a feeling of slight resistance and of grating if the blade is not very sharp The absence of this feeling is an indication that the blade is too far posterior, and must be avoided If indicated, the knife may be reversed and the stripping repeated in the opposite direction

If, on reexamination later, this goniotomy proves to have been insufficient, another stripping can be performed on an adjoining part of the angle after suitable rotation of the eyeball It has been possible in some cases, as shown by postoperative gonioscopy, to strip the angle over almost one-half its circumference at one sitting

Picking up the root of the iris and hemorrhage are the only serious complications against which one must guard It has been found that removal of blood from the anterior chamber by paracentesis and irrigation cannot be adequately accomplished in infants It is better to be obliged to repeat the operation than to provoke a major hemorrhage by placing the blade too far posterior or by attempting too extensive stripping If the stripping has been properly placed, a little blood of venous color begins to ooze from several points along the line of stripping a few seconds after removal of the knife If the head is rotated to the opposite side, the blood coalesces to a thin sheet in the region of the pupil and is seen to stop If the blood is more arterial in color, is more extensive and follows immediately on the incision, the puncture has been placed more posterior than is desirable Blood may fill one-half the chamber, it is usually absorbed within twenty-four to forty-eight hours

The canthotomy wound is sutured, medications are given and dressing is applied, as already outlined in the procedure under the glass

#### STRIPPING OF THE ANGLE

In congenital glaucoma, there is an area of from 2 to 3 hours in the circumference of the angle opposite the point of puncture in which it is easiest to do an adequate stripping Since the position of the puncture is limited on the right eye by the brow and on the left by the cheek bone, a point is chosen as far as possible in a clockwise direction

—for instance, on the right eye at 10 30 o'clock, in order to strike the opposite nasal angle as far clockwise as possible, i e, at 4 30 o'clock. When the blade has reached 2 30 o'clock, it has covered the area in which stripping can be done under optimum conditions and with least hazard. Postoperative gonioscopy shows that it is often possible to strip a more extensive area, up to 4 hours or more by the clock. Since this cannot be done consistently, and since it is associated with greater hazard of hemorrhage, it is well to consider allocating the area of the first stripping in such a way that another area of the angle, as yet untouched, can be stripped on a second occasion. For this purpose, it is advisable in either procedure, with or without the glass, to start with the eye rotated 2 hours in a counterclockwise direction. Thus, for operation on the right eye the bulb is rotated in a counterclockwise direction so as to bring the area of the nasal angle between 6 and 3 o'clock within operative reach. The assistant maintains the bulb in this position and resists, if necessary, the traction of the blade while it strips the angle in a counterclockwise direction. If later examination shows that the result of this procedure was not sufficient to normalize pressure, stripping of a neighboring area of the angle (from 3 to 12 o'clock) may be undertaken. In the latter case the right eye is rotated 2 hours in a clockwise direction to make the area accessible. The puncture is made at 10 30 o'clock, and stripping is performed from 5 to 3 o'clock in the rotated position, which corresponds to 3 to 1 o'clock when the bulb is in the normal position. It is possible, therefore, by means of two goniotomies, to strip the angle up to one-half its circumference, i e, from the 6 to the 12 o'clock meridian.

#### PRELIMINARY DEEPENING OF THE ANTERIOR CHAMBER WITH ISOTONIC SODIUM CHLORIDE SOLUTION

Preliminary deepening of the anterior chamber with isotonic sodium chloride solution U S P may be performed in cases in which operation is done without the glass in order to minimize the hazard of picking up the root of the iris with the tip of the knife. The chamber is not deepened for the operation under the glass, in this case the blade of the knife is guided under direct vision, and therefore picking up the root of the iris, with consequent hemorrhage, can be avoided. Deepening should be considered in the case of infants, especially those between the ages of several days to several weeks because of the relatively shallow chamber and narrow angle. It permits of a more deliberate placement of the stripping in regard to its anteroposterior position. However, it is well to dispense with deepening when possible, as it introduces a delicate technical detail which, if not adequately performed, may result in leakage of aqueous and postponement of the operation. When deepening is employed, great care must be taken in prelaying the corneal puncture

The bulbus is fixed with a Bishop Harman forceps at the opposite limbus. The cornea is punctured tangentially 1 mm axial to the corneoscleral border, at 9 o'clock on the right eye and at 3 o'clock on the left eye, with a discission knife, the blade of which has been previously dipped in fluorescein. The wound canal should be at least 3 mm long. The tip of the knife should barely perforate Descemet's membrane, as observed through a head loupe with a magnification of 5. It may be necessary to tip the knife backward a little in order to perforate this membrane. Care must be taken not to enlarge the puncture on removing the discission knife, lest leakage ensue. The puncture made visible by fluorescein is touched with a dry applicator and then one dipped in tincture of iodine, from which the excess has been removed. With a no. 30 needle (previously drum tested or examined under a loupe to assure its having a perfect point) attached to a 1.5 cc Luer syringe, saline solution is injected intravenously, the surgeon fixing the bulbus at the contralateral limbus with a Bishop Harman forceps.

#### AIR GONIOTOMY

If goniotomies have not reduced the pressure sufficiently and gonioscopy shows that further repetition of goniotomy in the nasal portion of the angle is not feasible because of adhesions of the iris or formation of scars, an attempt may be made to perform goniotomy under air in the temporal portion of the angle. This area can be made visible by filling the chamber with air.<sup>9</sup> Since it is difficult consistently to insufflate the whole anterior chamber with air through a corneal puncture, an oblique scleral incision similar to that for cyclodialysis is used and the sterile air injected by means of a curved gold cannula and a small Luer syringe. The eye is then fixated with two Gifford forceps with lock and abducted. The temporal limbus disappears behind the canthus. The operator stands on the opposite side. The knife is passed across the bridge of the infant's nose and the cornea punctured 1 mm axial to the nasal corneoscleral border. Goniotomy under air, or "air goniotomy," of the temporal portion of the angle is performed. Only a gross picture of the insertion of the root of the iris is discernible through air, owing to the opacities of the cornea, to reflections and to absence of magnification. However, visibility, when combined with familiarity of the angle, may be sufficient to act as a guide to the blade of the knife.

#### BLUNT DISSECTION

Blunt dissection of the angle with a spatula inserted through a pre-laid corneal puncture has been tried in place of stripping or peeling of the

<sup>9</sup> Barkan, O. Goniotomy, *Am J Ophth* **28** 1133-1134 (Oct.) 1945. Hughes, W. L., Technical Uses of Air in Ophthalmology, *Arch Ophth* **35** 525-540 (May) 1946.



angle with a goniotomy knife. In practice, this has shown no advantage over the present technic with the knife, on the contrary, it appears to encourage adhesion of the root of the iris and closure of the angle.

#### GONIOTOMY KNIFE<sup>10</sup>

The shaft of the knife is conoid in order to prevent loss of aqueous. Its diameter increases progressively from the tip of the blade to the heel of the shaft. The blade is not too sharp, as it is used to strip or peel, and not to incise, the tip being sharp enough to permit easy puncture of the cornea. The blade offers some resistance during the stripping, which gives the operator a feeling of guidance and deliberate movement.

#### SUMMARY

Goniotomy, which at the time of this writing had been performed on 76 eyes with infantile glaucoma, preserved useful vision in most cases. In 66 eyes pressure was normalized and vision maintained or restored over periods ranging from one to ten years. In 10 eyes the operation was unsuccessful. When combined with early diagnosis, it provided excellent visual results.

The mode of action of goniotomy is discussed.

The advantages and disadvantages, indications and contraindications of goniotomy are given.

The technic of goniotomy is described.

The importance of early diagnosis and prompt operation is stressed.

490 Post Street

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<sup>10</sup> The knife, surgical contact glass, in two sizes, and hammer lamp can be obtained from A. H. Parsons Laboratories, 442 Post Street, San Francisco (2). The knife will be obtainable also from E. Grieshaber, Schaffhausen, Switzerland. Recently specifications for its present form have been sent to V. Mueller and to Storz.

# USE OF PROPIONATES IN OPHTHALMOLOGY

## A Preliminary Report

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NEW YORK

THE PURPOSE of this paper is to acquaint ophthalmologists with a group of physiologic antibiotics, which have hitherto not been used in treatment of ocular infections, and which appear to have certain advantages over medicaments now in general use. This group consists of the lower fatty acids, which occur in the human body. In this preliminary report, the sodium salt of one of these fatty acids, sodium propionate ( $C_2H_5COONa$ ), was selected for study. While this paper is based essentially on clinical observations, a certain amount of laboratory investigation concerning sodium propionate has been made, and more is in progress. The drug has been used in about 400 cases of infections of the lids, conjunctiva and cornea, and the results so far have proved of sufficient promise to merit further trial.

The use of fatty acids in the treatment of mycotic infections was first introduced by Peck and his co-workers<sup>1</sup> in 1939. These investigators were led to this treatment because their work had convinced them that human perspiration serves as a protective coating against infections generally, and fungous infections in particular. The actual basis for their treatment was their demonstration that sweat was fungicidal and fungistatic because of its content of fatty acids. Previously, Peck and Rosenfeld<sup>2</sup> had shown that the fatty acids inhibited growth of pathogenic fungi and that many of them were even fungicidal in proper concentration. In this excellent piece of work, the fatty acids, beginning with formic acid, with one carbon atom, and going up to capric acid, with ten carbon atoms, as well as the unsaturated undecylenic acid, were studied for their fungicidal powers. It was noted that almost all the sodium salts were less fungicidal than their corresponding acids. Sodium propionate, however, was as effective as propionic acid, while sodium undecylenate was even more effective as a fungicide than its

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Read before the New York Academy of Medicine, Section of Ophthalmology, April 19, 1948

1 Peck, S M, Rosenfeld, H, Leifer, W, and Bierman, W. Role of Sweat as a Fungicide, *Arch Dermat & Syph* **39** 126-146 (Jan) 1939

2 Peck, S M, and Rosenfeld, H. The Effects of Hydrogen-Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, *J Invest Dermat* **1** 237-265 (Aug) 1938

acid, but was otherwise undesirable. Because of this fact, and for other practical considerations, Peck and his associates chose sodium propionate for clinical use, administered topically, and reported gratifying results in the treatment of fungous infections. For purposes of reference, the chemical formulas of the lower fatty acids are listed in table 1.

Following this work, Hoffman, Schweitzer and Dalby,<sup>3</sup> of the Ward Baking Company, demonstrated, in 1939, that many of the fatty acids and their salts are fungistatic for certain nonpathogenic fungi. Many of the large baking companies now incorporate sodium propionate in bread dough and cake batter to inhibit the growth of mold. This practically universal practice and other experimental data indicate that sodium propionate is not highly toxic. The retarding effect of propionates on molds in dairy products has also been under investigation by a number of workers.

TABLE 1—*Chemical Formulas of the Lower Fatty Acids\**

Carbon Atoms		
1	Formic acid	HCOOH
2	Acetic acid	CH <sub>3</sub> COOH
3	Propionic acid	CH <sub>3</sub> CH <sub>2</sub> COOH
4	Butyric acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> COOH
5	Valeric acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> COOH
6	Caproic acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub> COOH
7	Heptylic acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> COOH
8	Caprylic acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> COOH
9	Pelargonic acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> COOH
10	Capric acid	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>8</sub> COOH
11	Undecylenic acid (unsaturated)	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> CH = CH COOH

\* Each succeeding saturated fatty acid is obtained by adding an additional CH<sub>2</sub> (methyl) radical.

In 1943 Keeney<sup>4</sup> reported extensive laboratory studies on the fungistatic activity of sodium propionate for pathogenic fungi. It is interesting to observe that *Candida albicans*, *Torula histolytica*, *Coccidioides immitis* and *Blastomyces*, all pathogenic yeasts which at times involve the ocular tissues, as well as *Actinomyces bovis*, were among the fungi whose growth was inhibited by sodium propionate. Keeney also made clinical investigations with the drug. Continuing these studies with the fatty acids, Keeney and his associates,<sup>5</sup> in 1944, extended their investigations to

3 Hoffman, C., Schweitzer, T. R., and Dalby, G. Fungistatic Properties of the Fatty Acids and Possible Biochemical Significance, *Food Research* 4 539-545 (Nov-Dec) 1939

4 Keeney, E. L. The Fungistatic and Fungicidal Effect of Sodium Propionate on Common Pathogens, *Bull Johns Hopkins Hosp* 73 379-390 (Nov) 1943

5 Keeney, E. L., Ajello, L., Broyles, E. N., and Lankford, E. Propionate and Undecylenate Ointments in the Treatment of Tinea Pedis and an in Vitro Comparison of Their Fungistatic and Anti-Bacterial Effects with Other Ointments, *Bull Johns Hopkins Hosp* 75 417-439 (Dec) 1944

include the antibacterial effects of these drugs. They then apparently demonstrated that a propionate-propionic acid ointment mixture, containing 16.4 per cent sodium propionate and 3.6 per cent propionic acid, was superior in its antibacterial effect on *Staphylococcus aureus* (coagulase positive) and on beta hemolytic streptococcus to 10 per cent ammoniated mercury, 5 per cent sulfathiazole and 0.5 per cent thyrothrycin, as well as benzoic and salicylic acids. When compared with a penicillin ointment containing 500 units of the substance per gram, the propionate-propionic acid mixture was found to be as effective against the beta hemolytic streptococcus but less effective against *Staph aureus*. They also showed that while the propionic acid component played the major role in fungistasis and a lesser role in bacteriostasis, the sodium propionate portion was also of great importance in these effects, by breaking down when in contact with the skin to form propionic acid. Thus, Keeney and his co-workers confirmed the observations of Peck and his group that fatty acid therapy was of value with fungous infections and, in addition, apparently demonstrated an unanticipated antibacterial action. The fact that one preparation was exceedingly effective against both fungi and bacteria was held to be extraordinary.

Further dermatologic reports on fatty acid therapy have confirmed the clinical value of these drugs and have stressed the infrequency of drug sensitization as well. The therapy has also proved effective in eradicating dandruff, which is considered by some to be related to blepharitis. Intramuscular injections of sodium undecylenate have been administered, with no ill effects<sup>6</sup>. Intravenous injections of sodium caprylate have been used successfully in the treatment of endocarditis due to *C. albicans*<sup>7</sup>. Propionate jelly has been used successfully for mycotic vulvovaginitis<sup>8</sup>, relief from pruritus vulvae occurred in three days. Propionates have proved valuable in treatment of rectal conditions. An excellent summary of the entire subject of fatty acid therapy was published in 1947 by Peck and Russ,<sup>6</sup> who also demonstrated the efficacy of propionate-caprylate mixtures, both in vitro and in vivo, in this paper.

It is interesting to note that fatty acids are among the ether extractives of the conjunctiva and probably occur in the secretion of the meibomian glands, they must also be present in the glands of Moll in the lid margin, because they are modified sweat glands, as well as in the other sweat glands of the eyelids.

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6 Peck, S. M., and Russ, W. R. Propionate-Caprylate Mixtures in the Treatment of Dermatomycoses, *Arch Dermat & Syph* **56** 601-613 (Nov.) 1947

7 Peck, S. M. Personal communication to the author

8 Alter, R. L., Jones, C. P., and Carter, B. The Treatment of Mycotic Vulvovaginitis with Propionate Vaginal Jelly, *Am J Obst & Gynec* **53** 241-244 (Feb.) 1947

The investigations reported in this paper were undertaken at the suggestion of Dr Samuel M Peck. It was felt that nontoxic compounds occurring in the human body, with demonstrated fungistatic as well as bacteriostatic powers, which caused little or no irritation when used locally, might be of value in treatment of external diseases of the eyes.

#### LABORATORY DATA

The laboratory studies were made in collaboration with Dr Peck.

Figure 1 shows the bacteriostatic effect of a 0.1 per cent solution of sodium propionate on a suspension of *Staph aureus* (coagulase positive) containing 4,000 organisms per cubic centimeter. After two hours a strong bacteriostatic effect was apparent. In a similar experiment, no growth at all was noted after three hours. Figure 2 demonstrates the

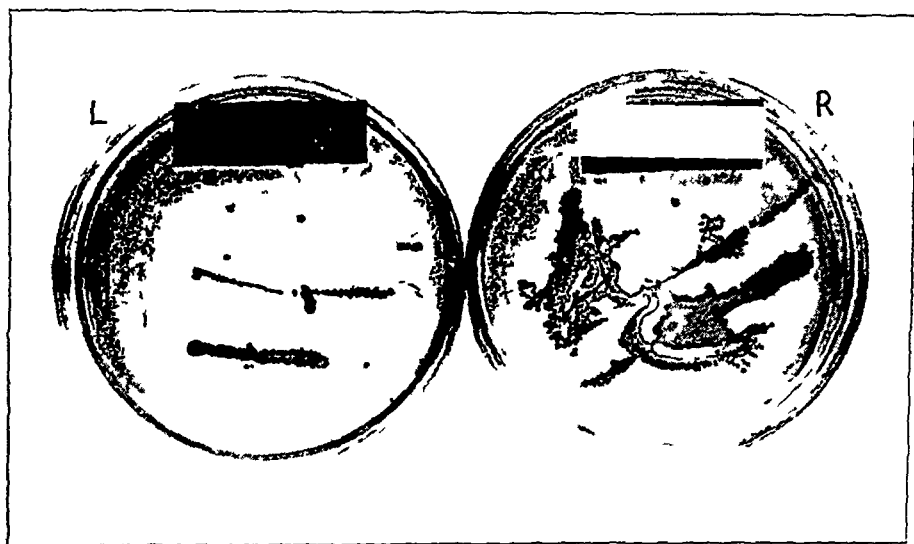


Fig 1—Bacteriostatic effect of a 0.1 per solution of sodium propionate on a suspension of *Staph aureus* (coagulase positive), containing 4,000 organisms per cubic centimeter. The picture on the right shows the growth when streaked after fifteen minutes' contact, the picture on the left shows the growth after two hours' contact.

antibacterial effect of 0.1 cc of a 5 per cent solution of sodium propionate, at  $p_H$  7.3, against coagulase-positive *Staph aureus* obtained from a patient with severe acute conjunctivitis, by means of the agar cup plate technic. The clear area about the cup represents the area of inhibition. Figure 3 *A* demonstrates the antibacterial effect against beta hemolytic streptococcus, and *B* shows well the effect against *Streptococcus viridans*. Figure 4 *A* shows that sodium propionate has an antibacterial effect on *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*), a finding of interest to ophthalmologists, *B* demonstrates its effectiveness against *Bacillus subtilis*, usually not an ocular pathogen. Figure 5 demonstrates how the antibacterial effect of sodium propionate increases greatly when used

in stronger solution or when 1 per cent sodium caprylate is added to it. Solutions of 5, 10, 15 and 20 per cent sodium propionate are used both alone and with 1 per cent sodium caprylate added to each. The agar

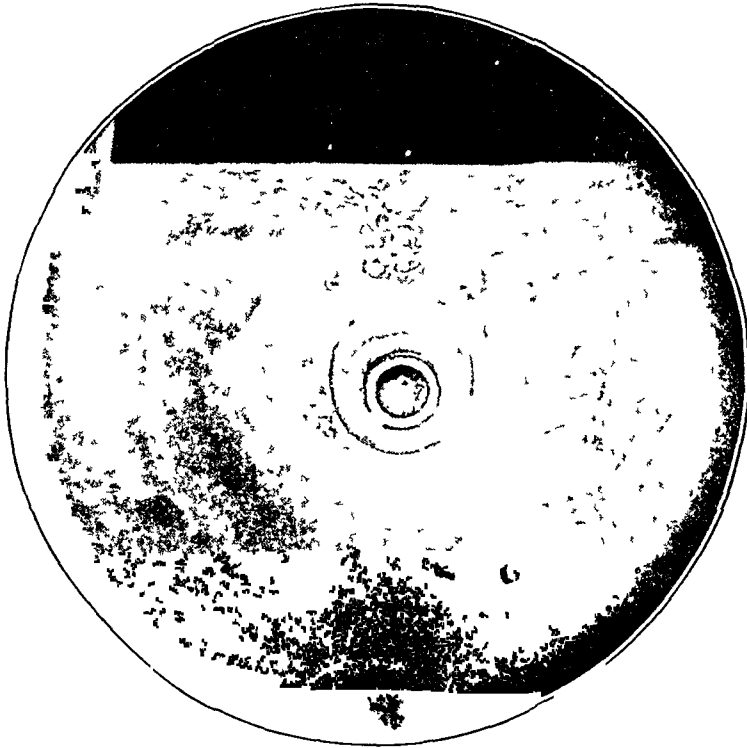


Fig 2—Bacteriostatic effect of 5 per cent sodium propionate at  $p_H$  7.3 on *Staph aureus* (coagulase positive), with agar cup plate technic. The clear area about the cup represents the area of inhibition.

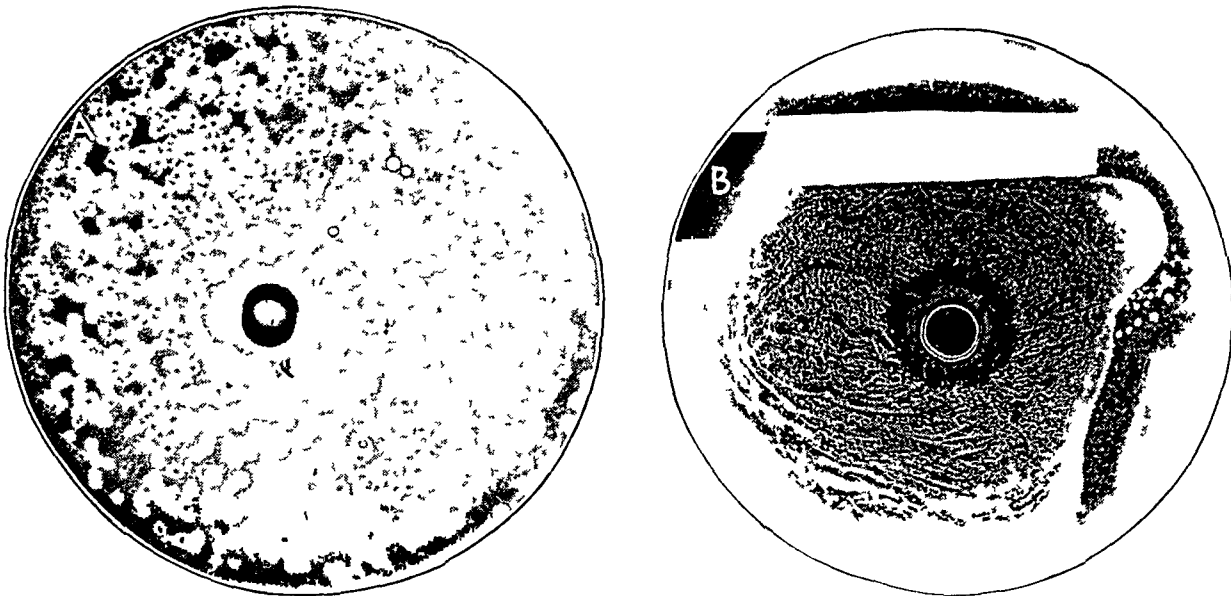


Fig 3—Bacteriostatic effect of 5 per cent sodium propionate at  $p_H$  7.3 on (A) beta hemolytic streptococcus, on (B) *Strep viridans*.

plates in this experiment contain an unusually heavy seeding of coagulase-positive *Staph aureus*.

It is to be noted that these experiments were carried out with the same solution as that used in the clinical studies, that is, 5 per cent sodium propionate at  $p_H$  7.3. The antibacterial and fungistatic effects of the drug increase greatly as the  $p_H$  becomes more acid.

#### CLINICAL RESULTS

For clinical investigations, a 5 per cent solution of sodium propionate, buffered to  $p_H$  7.3, was used.<sup>9</sup> In addition, an ointment containing the drug in 2 per cent concentration was also tried out, and a jelly containing 5 per cent sodium propionate is being tested. The ointment proved slightly irritating in some cases and is therefore not entirely satisfactory.

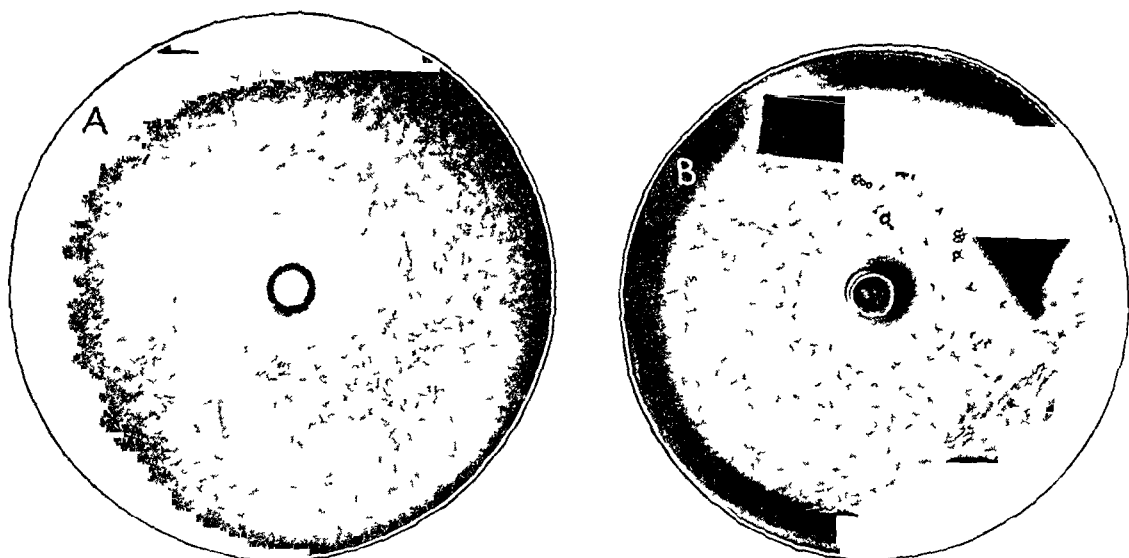


Fig 4—Bacteriostatic effect of 5 per cent sodium propionate at  $p_H$  7.3 (A) on *Ps aeruginosa* and (B) on *B subtilis*.

TABLE 2—*Clinical Results in Treatment of Acute Conjunctivitis with 5 Per Cent Sodium Propionate*

Type of Conjunctivitis	Total No of Cases	Improvement		
		Pronounced	Some	None
Acute Bacterial				
Staphylococcus A	53	47	4	2
Pneumococcus	6	6		
Hemophilus influenzae	1	1		
No culture or sterile culture	25	23		2
Acute Viral				
Béal's type	2			2
Epidemic keratoconjunctivitis	5			5

at present. The jelly is better tolerated. Clinical observations were made on private patients, in Dr R. Townley Paton's clinic at the

<sup>9</sup> The solution of sodium propionate used in the clinical studies was supplied by the Mycoloid Laboratories, Little Falls, N. J.

Manhattan Eye, Ear and Throat Hospital and in Dr Henry Minsky's service at the Mount Sinai Hospital. As the evaluation of clinical results is at best difficult, and of little worth unless exact diagnoses are made, bacteriologic studies were carried out whenever possible. These included differential cultures, secretion smears and epithelial scrapings of the conjunctiva and lid margins. Staphylococci were studied for

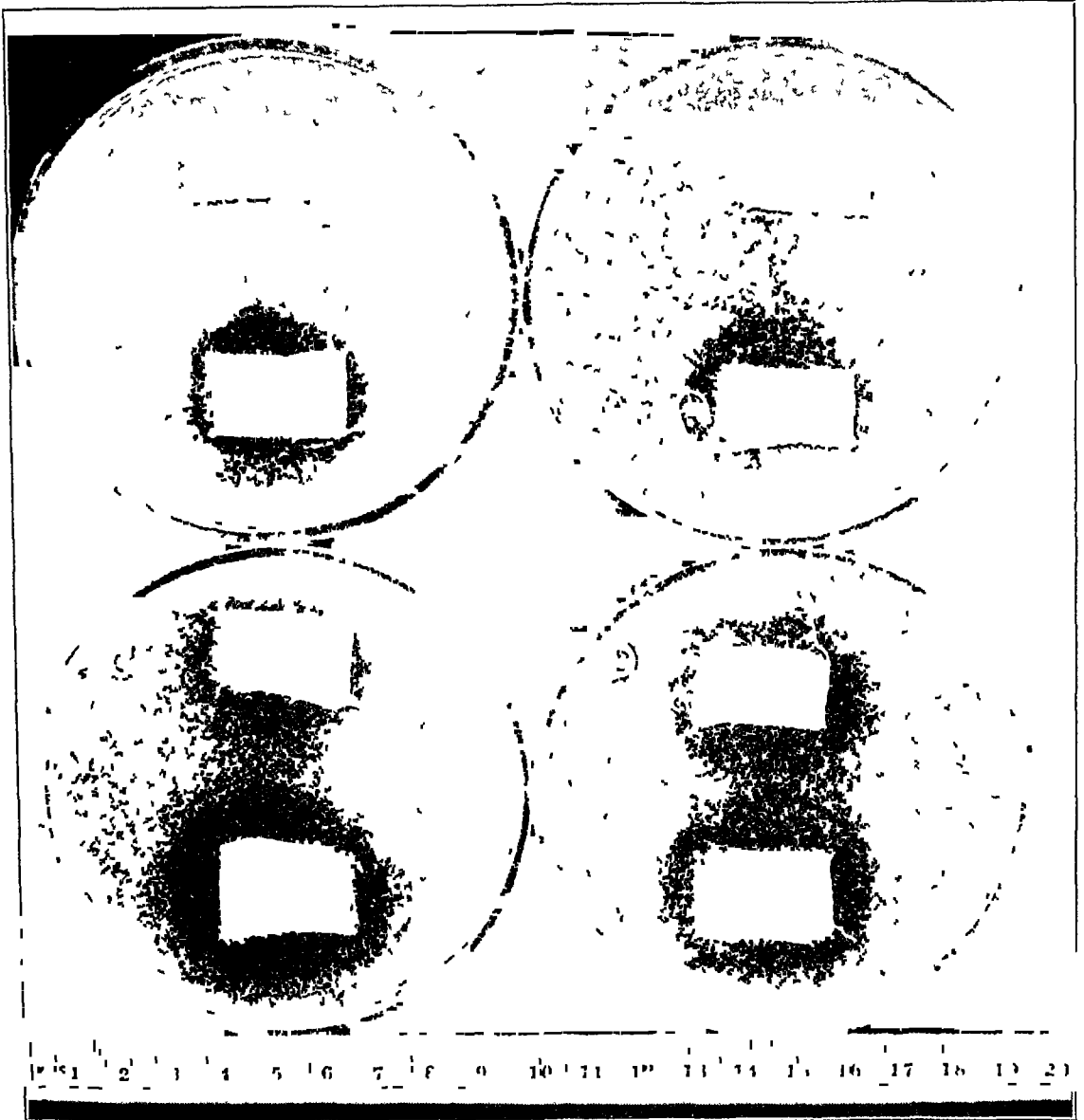


Fig 5—Bacteriostatic effects of higher concentrations of sodium propionate at  $p_H$  7.0 and propionate-caprylate mixtures on *Staph aureus* (coagulase positive). In plate A, the upper gauze contains 5 per cent sodium propionate, in plate B, 10 per cent sodium propionate, in plate C, 15 per cent sodium propionate, and in plate D, 20 per cent sodium propionate. The lower piece of gauze in each plate contains the same concentration of sodium propionate as the upper gauze plus 1 per cent sodium caprylate.

hemolysis, the coagulase reaction and the fermentation of mannitol. No attempt was made to select favorable patients for treatment; every patient seen was treated with sodium propionate.



*Acute Conjunctivitis*—Sixty patients with acute mucopurulent or purulent conjunctivitis whose cultures yielded pathogens were treated with 5 per cent sodium propionate solution every two or three hours. As indicated in table 2, the disease in 53 patients was due to *Staphylococcus A*,<sup>9a</sup> the toxic variety. Of these 53 patients, 47 became practically well in forty-eight to ninety-six hours. Four patients improved but needed special treatment, such as local applications of silver nitrate, to expedite their recovery. Six patients with pneumococcic conjunctivitis became well in forty-eight to seventy-two hours. A patient with an especially severe form, due to influenza, did well with propionate therapy. Of 25 patients with acute mucopurulent conjunctivitis for whom cultures were not made, or whose cultures were sterile, the condition cleared up rapidly in 23, in 2 it was not helped significantly by the drug. In some of these patients the disease was milder than the average severe form in the series whose cultures grew pathogens.

In 2 patients with acute follicular conjunctivitis (Béal type) the infection did not respond objectively to sodium propionate. The patients

TABLE 3—*Clinical Results in Treatment of Chronic Conjunctivitis with 5 Per Cent Sodium Propionate*

Etiologic Factor	Total No of Cases	Improvement		
		Pronounced	Some	None
Staph A	16	14	1	1
Pneumococcus	1	1		
Streptothrix	1		1	
Lacrimal conjunctivitis	3		3	
Keratoconjunctivitis sicca	1		1	

appeared more comfortable while using it, but the course was not shortened. In 5 patients with epidemic keratoconjunctivitis, likewise, the benefit was only subjective. Corneal opacities developed.

*Chronic Conjunctivitis*—In the series of 17 cases of chronic catarrhal conjunctivitis with positive cultures, unassociated with significant blepharitis, of the 16 cases in which *Staph A* was the causative agent, the patients were greatly improved, if not well, in 14. In the other 2 cases longer treatment was required. In these cases, incidentally, the infection did not respond to sulfacetimide and penicillin. In 1 case of pneumococcic conjunctivitis improvement was pronounced (table 3). In 3 cases of lacrimal conjunctivitis the conjunctiva became cleaner on the use of propionates. In 1 case of streptotrichal canaliculitis, the associated mucopurulent conjunctivitis improved under treatment with propionates, even before removal of the concretions. In a case of keratoconjunctivitis sicca associated with Sjogren's syndrome, considerable

9a. The term *Staphylococcus A* is used to denote either *Staph aureus* or a *Staphylococcus albus* which has been shown by tests to be toxic.

improvement, both subjective and objective, occurred with the frequent use of sodium propionate. The corneal erosions did not improve, however. In another, milder, case, the condition also improved.

*Chronic Infections of the Lid*—Chronic blepharoconjunctivitis, which has been stated by Thygeson<sup>10</sup> to be due either to a toxic staphylococcus or to the yeast *Pityosporum ovale* or to a combination of the two, seemed to offer an exceptionally good field for trial of the fatty acids. Not only may the administration of a therapeutic agent which is fungistatic, as well as antistaphylococcic, be useful in itself, but the well known chronicity of the condition makes eventual drug sensitivity and bacterial resistance not unusual. Treatment was started with sodium propionate, in the form of drops of the 5 per cent solution and the 2 per cent ointment. As soon as the initial effect of this drug was noted, the treatment was broadened in the severest cases to include applications of silver

TABLE 4—*Clinical Results in Treatment of Chronic Infections of the Lid with 5 Per Cent Sodium Propionate*

	Total No of Cases	Improvement		
		Pronounced	Some	None
Blepharoconjunctivitis				
Staph. A	27	19	6	2
Staph. A and yeast	12	10	2	
Infectious eczematoid dermatitis				
Staph. A	5	3	2	
Meibomitis with recurrent chalazions				
Staph. A	3	3		
No pathogen found	1			1

nitrate and injections of staphylococcus toxoid. It is perhaps unnecessary to emphasize that the use of a drug by the patient alone usually will not suffice in a case of chronic blepharoconjunctivitis of any severity. As is well known, the condition generally requires considerable local treatment by the ophthalmologist and desensitization by injections in severe cases if toxic staphylococci are present. Of the patients who did well, at least one-half had previously used penicillin and sulfonamide drugs but could not tolerate them for long periods. Several patients whom these drugs had not helped at all did remarkably well with propionates from the start.

As shown in table 4, in all the 39 cases of chronic blepharoconjunctivitis Staph. A was the causative agent. In addition, in 12 cases yeast organisms were found in significant numbers in scrapings of the lid margins. In the latter group the response appeared to be somewhat better than in the group in which no yeasts were found. Follow-up scrapings in the group with yeast infections revealed notable diminu-

<sup>10</sup> Thygeson, P. Etiology and Treatment of Blepharitis, Arch. Ophth. 36:445-477 (Oct.) 1946.

tion in most cases, in some even absence of the yeast organisms after treatment. However, in at least 1 case, with clinical recovery, great numbers of yeast organisms were still present. In 1 of the 2 cases of failure in the entire series, penicillin and the sulfonamide drugs did not help either, in the other case, sulfacetamide definitely improved the condition temporarily but could not be tolerated later.

Of 5 cases of infectious eczematoid staphylococcal dermatitis, great improvement occurred in 3, and some improvement, but not complete, was noted in 2.

In all 3 cases of chronic meibomitis with recurrent chalazions in which Staph. A was grown, the condition improved to a notable degree, and it responded to the complete type of treatment used with blepharitis. In the other case, in which no pathogen was found, the infection was not helped by propionates or by any of the antibiotics, but did respond to roentgen therapy.

TABLE 5—*Clinical Results in Treatment of Corneal Infections with 5 Per Cent Sodium Propionate*

	Total No of Cases	Improvement		
		Pronounced	Some	None
Catarrhal ulcers				
Staph. A	6	4	1	1
Culture sterile	2	1		1
Rosacea keratoconjunctivitis	2	2		
Dendritic keratitis	1			1
Mooren's serpiginous ulcer	1			1

*Corneal Infections*—Of 8 cases of catarrhal corneal ulcers observed, Staph. A was isolated from the conjunctiva in 6 (table 5). Of these 6 cases, striking improvement with propionates occurred in 4, some improvement in 1 and no improvement in 1. In the last case the ulcer did not respond to penicillin either, but required use of the thermaphore. In 1 case in which the culture was sterile, a good response also occurred. In the other, a case of recurrent ulcer, the condition was not significantly influenced by either penicillin or propionates and may have had an allergic origin. In those cases in which the propionates did not help objectively, they seemed to alleviate subjective symptoms.

In 2 cases of rosacea keratitis with intense conjunctival inflammation, considerable improvement occurred with sodium propionate.

In a case of herpetic (dendritic) keratitis sodium propionate was of no benefit. However, after extensive cauterization with iodine, propionate jelly was found to be soothing and did not appear to interfere with healing. In a case of Mooren's serpiginous ulcer the lesion was entirely uninfluenced by the drug.

*Miscellaneous Conditions*—In addition to the 174 cases just discussed, all of which were carefully classified etiologically, sodium pro-

pionate was used in about 200 cases of chronic conjunctivitis of varying degrees of severity in which either cultures and scrapings contained no pathogen or cultures were not made because the condition was not severe enough to warrant it. In many of these cases, significant objective improvement was noted, moreover, in many others the patient noted subjective improvement and requested more of the medicine. The fact that a number of them had not reacted as well to the usual medications prescribed lent more importance to this favorable subjective response. This effect has also been noted in the use of propionates on other mucous membranes, as well as dermatologically.

In a case of an extensive burn of the cornea with lye, the patient was comfortable with the use of sodium propionate drops, and epithelization did not appear retarded.

*Allergy*—In the entire series of 400 cases, a mild reaction suggestive of sensitivity developed in 1 case. In some cases transient minor irritation developed, but the use of the drug was continued.

#### CONCLUSIONS

Preliminary studies appear to indicate that sodium propionate may be of value in the treatment of external diseases of the eyes. It seems efficacious in the usual types of acute bacterial conjunctivitis encountered and plays a useful role in the treatment of chronic blepharoconjunctivitis and other types of chronic infections of the lid. It is a nontoxic, nonirritating, physiologic drug, which apparently may be tolerated for months without the development of drug sensitivity, except in rare instances. Most patients find it soothing to use. Although its antibacterial spectrum has not yet been completely delineated, there is evidence, both clinical and laboratory, that the bacteria which generally cause ocular infections are sensitive to sodium propionate. It appears to be of value in some cases in which the sulfonamide compounds and antibiotics no longer are effective. The reverse also occurs. It is ineffective in treatment of virus infections of the eye.

In a self-limited infection, such as acute bacterial conjunctivitis, good results will be obtained from many medicaments. Since the advent of the sulfonamide drugs and antibiotics, one is likely to forget, for example, the value of silver, both mild silver protein U.S.P. and silver nitrate, in treatment of this condition. Just what is used is of less moment in conditions of this type, except of course in the hyperacute types of infection, such as those due to the gonococcus or the meningococcus. In the case of the average acute infection almost any thing will be of help sooner or later. However, sodium propionate appears efficacious in about as short an interval as any other drug used and seems to have no unpleasant sequelae. Furthermore, owing to its effect on staphylococci, its use

should diminish the tendency of acute staphylococic conjunctivitis to become chronic

In cases of the chronic type of blepharoconjunctivitis the choice of medication becomes of greater importance. In this condition, it would appear that the use of sodium propionate may be of particular value. Although Keeney found a 20 per cent propionate-propionic acid ointment to be more effective than the sulfonamide compounds, and only slightly less effective than penicillin, *in vitro*, the 5 per cent solution of sodium propionate at  $p_H$  7.3 was less effective *in vitro*. However, *in vivo*, 5 per cent sodium propionate is usually equally effective, even sometimes superior, probably owing to its prolonged action. The clinical shortcomings of the sulfonamide drugs and the antibiotics, including penicillin, streptomycin and tyrothricin, became more apparent in treatment of chronic blepharoconjunctivitis. The frequent allergies that occur, and the development of bacterial resistance, which may persist for years, are among the important drawbacks to their prolonged use. Furthermore, these drugs have little effect against most fungi, including yeast. Thus the combination of fungistatic and antibacterial action that sodium propionate appears to offer suggests that further studies concerning it may be worth while, even if it proves to be of value merely as another supplementary method of treatment or when combined with other drugs. The fact that sodium propionate can be safely and effectively used after the sulfonamide drugs and the antibiotics have been tried, and have caused irritation, is alone of great therapeutic usefulness.

The favorable results noted occurred with a 5 per cent solution of sodium propionate buffered to  $p_H$  7.3. As the drug is more effective *in vitro* at an acid  $p_H$ , and as concentrations higher than 5 per cent appear to be tolerated in the eye and have greater antibacterial effect, studies are now in progress to determine what strength and what  $p_H$  will prove the most effective clinically. A combination of propionates with caprylates is also being tried.

Further studies of the scope of usefulness of fatty acid derivatives administered internally or parenterally may indicate value in fungous infections of all the ocular tissues. The use of the drugs as preservatives for ocular medicaments may also be found advantageous.

#### SUMMARY

The lower fatty acids are nontoxic, physiologic antibiotics and fungicides. Sodium propionate, a fatty acid derivative, was used clinically in about 400 cases of conjunctivitis, blepharitis and keratitis. It has proved efficacious and nonirritating, especially in treatment of chronic conditions, and shows promise in its use as a supplement or substitute for other therapeutic agents now in general use.

# Abstracts from Current Literature

EDITED BY DR WILLIAM ZENTMAYER

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## Anatomy and Embryology

THE VARIATIONS IN THE SYSTEM OF THE TRUNKS OF THE POSTERIOR CILIARY ARTERIES T SUDAKEVITCH, *Brit J Ophth* 31:738 (Dec ) 1947

The author notes the absence in the textbooks of ophthalmology of a special section to describe the constant anastomoses of the ophthalmic artery, or, of more importance, the pathologic changes in the eye connected with them, notwithstanding that there is no lack of scientific investigation of these anastomoses, they have been well known for a long time. A review of the known variations in the system of the ophthalmic artery is then given, followed by the author's anatomic studies. Special attention is given to the two most essential points—the system of the ophthalmic artery in the orbit itself and its part within the skull. What the author believes to be heretofore undescribed is the fact that the ophthalmic artery forms an angle when it passes around the optic nerve, before it enters the foramen opticum—first below it and externally, then to the superior external margin and then toward the medial side, crossing the optic nerve from above. This angle exists nearly always. As a rarity it may be absent—for instance, when the ophthalmic artery is situated below and to the medial side of the optic nerve. The angle is not always the same, not only in different persons, but even in the same person. In childhood and adolescence the angle is always sharp; after the age of 24 it is chiefly perpendicular, and after 40 years of age it is obtuse. The sharp angle may be preserved, in single instances, up to senility, but it is not seen after the age of 65.

The author thinks that no one has previously described this angle, but the variations in it that are due to age change the correlations of various parts of the ophthalmic artery, and so the direction of the pulse wave, for the artery in this particular spot is always firmly fixed to the membranes of the optic nerve and cannot straighten its angle each time in relation to the pulse wave. It is for this reason that the angle changes with age from a sharp to an obtuse one.

The article does not lend itself well to abstracting. It is accompanied with 28 illustrations.

W ZENTMAYER

STUDY OF PIGMENT CELLS OF THE CHOROID IN THE CHICK EMBRYO. J NORDMANN and R STOLL, *Ophthalmologica* 114:99 (Aug ) 1947

In chick embryos, the pigment cells of the choroid can be recognized from the tenth day after fertilization. These cells are independent of the pigment layer of the retina from the beginning, and some of the cells show a close relationship to the choroidal nerve endings. The authors point out that pigmentary elements are usually developed in close relationship to such innervation.

F H ADLER

### Conjunctiva

FURTHER RESEARCH ON PANNUS FOLLICULARIS TRACHOMATOSUS  
C PASCHEFF, *Am J Ophth* 30:1001 (Aug) 1947

Pascheff concludes that pannus is a lymphofollicular hyperplastic manifestation or reaction of the limbal conjunctiva and has the same histologic structure and evolution as that in trachoma verum. The best way to avoid recurrence is to transplant skin instead of mucous membrane.

W S REESE

CONJUNCTIVITIS WITH MEMBRANE FORMATION M J HOGAN, *Am J Ophth* 30:1495 (Dec) 1947

Hogan presents a classification of types of conjunctivitis in which membranes develop and discusses the nature and pathogenesis of this membrane formation. Diphtheroids from 100 cases of external ocular disease were studied for pathogenicity. Attempts to enhance the pathogenicity of diphtheroids by utilizing the protective effect of mucin were unsuccessful, as were attempts to produce diphtheroid infections of the conjunctiva by lowering the resistance of the conjunctiva with diphtheria toxin and trauma.

W S REESE

### Cornea and Sclera

ANTITOXIN TREATMENT OF STAPHYLOCOCCIC CORNEAL ULCERATION  
J H ALLEN, *Am J Ophth* 30:987 (Aug) 1947

Allen concludes that administration of antitoxin is of practical value as a temporary measure in the treatment of severe staphylococcic infections until active immunization, chemotherapy or antibiotic therapy can become effective.

W S REESE

GRAVE MANIFESTATIONS OF GOLD THERAPY IN THE CORNEA AND SKIN  
U AZZOLINI, *Riv di oftal* 1:361, 1946

The author describes a case in which tuberculous manifestations were favorably influenced over several years by two series of gold treatments. At the start of the third series, grave changes occurred in both corneas and the skin of the face, associated with a high degree of eosinophilia.

After reviewing the modern concept of allergy and parallergy and considering the reaction which appeared in the cornea and the skin after the administration of a gold salt, the author asserts that a local sensitivity develops and is due to the sum total of tissue changes of a parallergic variety brought on by successive series of gold therapy. The eosinophilia places this reaction in the group of pseudoidiosyncrasies.

G B BIETTI—J J Lo PRESTI

BLOOD STAINING OF THE CORNEA W A MANSCHOT, *Ophthalmologica* 113:203 (April) 1947

Five cases of blood staining of the cornea are reported, in which histologic sections were made and certain histochemical tests were carried out. The author points out that blood staining of the cornea may

occur as a ring, instead of the disk generally reported. Blood staining of the cornea occurs only after trauma or glaucoma, so that it is probable that preceding damage of the endothelium and of Descemet's membrane is necessary for its appearance. In almost all of the cases which have been studied anatomically, highly refractile oval bodies are observed within the cornea. These were first described by Treacher Collins. The author found that they are digested by trypsin, and hence he believes that they consist of the crystalline precipitation of the protein bodies of hemoglobin. The pigment observed in the protoplasm of the corneal cells contains iron as well as fat, so that it is obvious that both hemosiderin and lipofuscin are present.

F H ADLER

### Experimental Pathology

INFLUENCE OF LOCAL ARTERIAL BLOOD PRESSURE ON AQUEOUS HUMOUR AND INTRAOCULAR PRESSURE. AN EXPERIMENTAL STUDY OF THE MECHANISMS MAINTAINING INTRAOCULAR PRESSURE. E. BÁRÁNY, *Acta ophth* 24: 337, 1946, 25: 81, 1947.

The author summarizes his study as follows. During the first twenty-four hours after closure of the carotid artery, the intraocular pressure and the blood pressure keep a level which does not differ from that attained one hour after closure of the artery. During the subsequent days a slight additional fall in blood pressure, and possibly also in intraocular pressure, is followed by a return to normal. This return to normal is much more rapid in the case of the intraocular pressure than in that of the blood pressure. Moreover, the intraocular pressure returns to complete normality in spite of the persistence of a considerable deficit in blood pressure. This return could be interpreted as the result of a slow-acting regulation. However, the fact as the intraocular pressure and the regulatory mechanisms completely recover, in spite of persistent deficit in blood pressure, supports the view that the observed regulation is an instance of a more general adaptation of the vascular bed to low blood pressure.

O P PERKINS

### General

ERUPTIVE FEVER WITH INVOLVEMENT OF THE RESPIRATORY TRACT, CONJUNCTIVITIS, STOMATITIS AND BALANITIS. S. N. SOLL, *Arch Int Med* 79: 475 (May) 1947.

This syndrome has been described under a variety of terms, such as eruptive fever with stomatitis and ophthalmia, erythema multiforme exudativum of Hebra, erythema or herpes iris conjunctivae, ectodermosis erosiva pluriorificialis and Stevens-Johnson syndrome. Soll reports observations on 20 cases occurring in military personnel. The disease is acute, probably infectious, self limited and febrile. Prodromal symptoms referable to the respiratory tract are followed by lesions of the skin and mucous membrane of the mucocutaneous junctions, characterized by vesicles and pseudomembranes and accompanied frequently with fever, and occasionally with bronchopneumonia. In determining the pathogenesis, bacteriologic observations are of no significance. There is no evidence that ingestion of drugs is a factor. Because of the prodromal symptoms referable to the respiratory tract and generalized manifesta-



tions, the disease is regarded as air borne, systemic and probably due to a virus. The various names proposed and used are misleading in that they direct attention almost exclusively to the skin. *Erythema exudativum multiforme* means little in cases in which dermatologic lesions do not occur. The term "*erythema pluriorificialis exudativum*" is better in that it refers also to the orifices of the body, but it is too long and has only descriptive meaning. Until the causative agent is found, appropriate naming of the disease will not be possible.

W ZENTMAYER

### General Diseases

SYNDROME OF SJOJREN E HARTMANN and S DE SEZE, Bull Soc d'opht de Paris, January-February 1947, p 10

According to the authors, these are the first 2 cases of Sjogien's syndrome seen in France. The triad of symptoms consist of evolutionary chronic arthritis, hyposecretion of salivary glands and secondary alterations of the conjunctiva and cornea with hyposecretion of the lacrimal glands and keratoconjunctivitis sicca. In both cases in which the syndrome was present the lower cul-de-sac was red and presented many follicles. A mucopurulent secretion revealed *Staphylococcus albus*. The cornea was cloudy and showed streaks which stained with fluorescein. The lacrimal secretion was diminished. There were a slight elevation of general temperature, partial anemia, and increase in polymorphonuclear cells.

L L MAYER

RELATION OF CUTANEOUS DISEASES AND OCULAR LESIONS M ARTOM, Rev paulista de med 29. 261 (Oct ) 1946

When one is considering the relation of the skin and the eyes, the pathologic condition of the eyelids and that of the globe should be studied separately. Quincke's angioneurotic edema and toxicodermal edemas, especially those caused by hair dyes, commonly involve the eyelids. Blepharitis establishes the patient's seborrheic condition. Dermatoses, such as zoster, lupus erythematosus, infections, burns, vaccinia pustules, trauma and mycosis, are of special importance when seen on the lids, as they often cause cicatricial ectropion. Xanthelasma is also of interest in connection with the cutaneous metabolism of the lipids. Syphilis and leprosy cause many ocular manifestations. Cutaneous tuberculosis is generally accompanied with ocular alterations, and phlyctenular keratitis is often observed in the several varieties of tuberculosis, especially the papulonecrotic type. Some cutaneous avitaminoses are characterized by ocular symptoms, such as the corneal lesions associated with pellagra, xerophthalmia and day blindness, which, in children, often accompany cutaneous manifestations characteristic of avitaminosis, and conjunctival and retinal hemorrhages, which are a part of the cutaneous syndrome of scurvy and avitaminosis C. Congenital cataract, which frequently accompanies the genodermatoses, that is, the alterations of the tegument and its adnexa caused by hereditary disturbances of the germ plasma, should be especially mentioned. Congenital cataract is also noted in association with Pringle's nevus and Recklinghausen's neurofibromatosis. Retinal angiod streaks, abnormalities of motility, exophthalmos and the condition of the fundus of the eye are considered.

M E ALVARO

## Glaucoma

THE PROBLEM OF GLAUCOMA JAN VANYSEK, Brit J Ophth 30:742 (Dec ) 1946

The author agrees that the comparison of glaucoma and edema is justified to a great degree. In an effort to find out whether there is a parallel between edema and glaucoma, he reviews present views on edema. One can easily find a parallel between inflammatory edema and glaucomatous iritis. In the typical secondary glaucoma which occurs in cases of thrombosis of the central vein of the retina, he finds a parallel with cardiac edema. For primary glaucoma he finds a parallel in Quincke's edema. In view of this concept of the pathogenesis of glaucoma, it would seem possible to control glaucoma in a conservative way by restoring the imbalance of the vegetative nervous system, paralyzing the sympathetic fibers and removing accentuating causes.

W ZENTMAYER

GENERAL AND LOCAL NEUROVEGETATIVE SYSTEM IN PATIENTS WITH PRIMARY GLAUCOMA MIGUEL DE TORRES LUCENA, Rev españ. de oto-neuro-oftal y neurocir 4:166 (Sept-Oct ) 1945

De Torres Lucena first studies the general tonus of the vegetative system in his patients with primary glaucoma. He subjects the patient to conditions similar to those necessary for a determination of the basal metabolic rate, repeatedly takes the patient's pulse in a clinostatic and an orthostatic position, injects neutral atropine sulfate, 0.25 mg, intra-venously and repeats the injection until a complete block of the vagal system is obtained. The frequency of the pulse at this point will indicate the sympathetic tonus, and its difference from the normal pulse rate gives the parasympathetic tonus. He found a constant dystonia (imbalance of the two parts of the vegetative system) in his glaucomatous patients: amphotony (increased tonus of both parts of the vegetative system) with acute congestive glaucoma and a mixed type with chronic simple glaucoma. He gives the following figures for patients with acute congestive glaucoma: amphotony in 65.51 per cent, a hypervagotonic-hyposympathicotonic state in 24.13 per cent, a hypersympathicotonic-hypovagotonic state in 6.89 per cent and a hyposympathicotonic state in 3.44 per cent, for chronic simple glaucoma: a hypervagotonic-hyposympathicotonic state for 50 per cent, a hypersympathicotonic-hypovagotonic state for 35.71 per cent, a hypersympathicotonic state in 7.14 per cent and a hypovagotonic state in 7.14 per cent.

Once his patient's vagal system was blocked, he determined the local tonus of the ocular sympathetic system by measuring the size of the pupil and taking the intraocular tension. In normal subjects no change in tension was observed, but in patients with primary glaucoma he obtained hypertension in 47.72 per cent, hypotension in 36.36 per cent and unaltered tension in 15.9 per cent. He considers these changes in tension an expression of a local dystonia of the ocular vegetative system, which is of sympathicotonic type in 50 per cent and of parasympathicotonic type in 30 per cent of patients with acute congestive glaucoma. He reached similar conclusions for simple chronic glaucoma.

ESCAPINI HUMBERTO

## Injuries

THE FUNDUS IN FRESH GUNSHOT WOUNDS OF THE SKULL S ZBARSKY, J Ophth 1. 43, 1946

Five hundred and thirty service men with trauma of the skull were observed, of these the meninges were injured in 80, the bones of the skull in 100 and the soft tissue of the brain in 350. The fundus was examined two to three days after the injury and every four or five days thereafter for three or four weeks, or as long as the patient remained in the hospital. Zbarsky summarized his observations and reached the following conclusions. Primary edema of the brain, even in cases of severe trauma of the skull, did not effect the optic nerve, the changes in which were observed on the third day. Papilledema appeared in cases of severe edema or infection of the brain. Of the cases of injury to the soft tissues of the head, the optic nerve remained normal in 100 per cent, of cases of injury of the bones of the skull, a pathologic condition of the fundus was found in 20 per cent, and in cases of injury of the brain, papilledema was observed in about 60 per cent. Papilledema was seen in 20 per cent of cases of traumatic abscess of the brain. A normal fundus usually indicated a favorable course of the injury to the skull and brain. The prolonged presence of papilledema in cases of prolapse of the brain is a poor prognostic sign. The picture of the fundus has an important diagnostic and prognostic value and will aid in deciding whether to perform an emergency operation or to evacuate the injured man from the Army base hospital to the rear.

Case histories illustrate the article

O SITCHEVSKA

## Lacrimal Apparatus

TECHNICAL CONTRIBUTIONS TO DACRYOCYSTORHINOSTOMY B CARRERAS DURAN, Arch Soc oftal hispano-am 6: 1134 (Nov) 1946

The author points out the danger of injury to the nasal mucous membrane when, in dacryocystorhinostomy, the opening in the bone is made with the trephine. To avoid this complication, he injects by the nasal route 1 or 1.5 cc of an oily solution of procaine hydrochloride between the nasal mucous membrane and the bone. Since the ophthalmologist is not familiar with the intranasal anatomy, the author has devised a simple instrument to point to the region where the injection is to be made. It consists merely of a metal rod, of the same length as the needle of the syringe, attached to the base of the needle and running parallel to it. The needle extends into the nose, and the rod remains on the outside. When the tip of the rod reaches the region of the lacrimal sac, the liquid is injected under the intranasal mucous membrane.

The danger of hemorrhage during or after dacryocystorhinostomy is minimized by making the incision in the nasal mucous membrane with a fine electric knife, instead of with the ordinary scalpel. The article is illustrated with drawings.

H F CARRASQUILLO

AN ADVANTAGEOUS MODIFICATION OF DACRYOCYSTORHINOSTOMY M BURCH BARRAQUER, Arch Soc oftal hispano-am 6 1150 (Nov) 1946

One of the most important causes of failure of dacryocystorhinostomy is closure of the opening made into the nasal cavity when the posterior

and anterior lines of sutures between the wall of the sac and the nasal mucous membrane come in contact and fuse in healing. To avoid this, the author has used to advantage in 29 cases a V-shaped silk suture, which, by being passed through the skin, nasal mucous membrane and wall of the sac and being brought out again through the skin, approximates the anterior wall of the sac and the anterior lip of the opening into nasal mucous membrane and brings them in contact with the superficial tissues when the ends of the thread are tied on the surface of the skin. In this way, the approximation of the suture of the posterior wall of the sac and the nasal mucous membrane and that of the anterior wall of the sac and the nasal mucous membrane is avoided.

The author uses a special technic for the incision in the skin and the dissection of the underlying muscle fibers and tendons in exposing the lacrimal sac in order to obtain the best results with his suture. At the same time, he achieves better cosmetic results.

H. F. CARRASQUILLO

### Methods of Examination

INVESTIGATION IN VARIABLE MONOCHROMATIC LIGHT OF THE OUTER VESSELS OF THE EYE. T. KORNERUP, *Acta ophth* 24: 423, 1946

The author's summary follows:

The pericoineal injection in eyes showing inflammatory changes was examined by the author in variable monochromatic light.

The so-called LS value, being the mean between the long wavelength (L) at which the vascular network close to the corneal limbus disappears and the short wavelength (S) at which it reappears, could thus be determined.

This value varies during the course of inflammatory diseases of the eye. A clinically observable, continuously proceeding improvement is accompanied with steadily falling LS values, a deterioration, by rising LS values, without any tendency to fall.

In several cases, as shown by the graphs, a change which was not yet clinically observable was predicted by a change in the LS values.

O. P. PERKINS

### Ocular Muscles

THE PSYCHOLOGY OF THE SQUINTER. A. E. STROMBERG, *Am J Ophth* 30: 601 (May) 1947

Stromberg concludes that the success of orthoptic training is determined by the desire and will of the patient to learn and that the development of this will depends on the teaching ability of the orthoptist. These patients must always be regarded as individual persons, not cases.

W. S. REESE

WHICH SQUINTS RESPOND BEST TO ORTHOPTIC TREATMENT? E. ROTH, *Am J Ophth* 30: 748 (June) 1947

Roth states that purely accommodative squints and those with a large convergence insufficiency factor offer a good prognosis, but that squints with a pure, or even a primary, divergence excess factor must be treated surgically.

W. S. REESE

THE PLACE OF PERIPHERAL FUSION IN ORTHOPTICS H M BURIAN,  
Am J Ophth 30:1005 (Aug) 1947

Burian discusses the various types and degrees of fusion and emphasizes the importance of studying the sensory behavior of the peripheral, as well as the central, areas and the training potentialities of the periphery of the retina

W S REESE

OPTIC NEURITIS AND OCULOMOTOR PARALYSIS A GRIGNOLO, Boll  
d'ocul 24:61, 1945

The author describes the case of a woman aged 48 in whom, after a typical eruption of herpes zoster ophthalmicus involving the first and second branches of the trigeminal nerve, there appeared three days later ptosis of the upper lid, paralysis of the superior rectus muscle, herpetic keratitis and retrobulbar neuritis, with complete loss of central vision and pallor of the nerve head. With the passing of time the paralysis of the levator and superior rectus muscles disappeared, but vision remained affected, owing to well established atrophy of the optic nerve

G B BIETTI

### Orbit, Eyeball and Accessory Sinuses

EXOPHTHALMOS IN RELATION TO ORBITAL TUMORS REPORT OF EIGHT  
CASES S B FORBES, South M J 40:206 (March) 1947

Eight cases of unilateral exophthalmos resulting from orbital tumors are reported. The series comprised a lipoma, an extraorbital squamous cell carcinoma involving the posterior part of the orbital plate, an ethmoidal pyocele, an ethmoidal mucocele and a primary pseudotumor, 1 case each, orbital hemangioma, 2 cases, and tremendous hypertrophy, edema and infiltration of the muscular cone and extraocular muscles, particularly the inferior rectus, 1 case. In the case of the primary pseudotumor, the exophthalmos disappeared after irradiation. In all the remaining cases surgical treatment was successful. The Kronlein operation was used for the removal of the hemangioma in both cases. However, the author experienced a great deal of difficulty with this approach in 1 of these cases, in which the hemangioma was situated in the extreme posterior inner aspect of the orbit, he states the belief that an approach through the brow or a transfrontal approach through the orbital roof would be easier and safer in cases of tumor in this location. An original method of delivering a large hemangioma *en masse* is described.

C P GRANT

PSEUDOSINUSITIS OF THE NEWBORN AND THE YOUNG INFANT G  
OFFRET and J MEAUX, Arch d'opht 7:250, 1947

This is a long, detailed discussion, with the citation of 2 cases. The development of the teeth and sinuses in the baby is presented in some detail. As a result of their investigation, the authors express the belief that the condition (pseudosinusitis) is primarily osteomyelitis of the superior maxilla. They state that the idea of a sinus origin in children should be abandoned. Formerly the prognosis was unfavorable, the

mortality reaching as high as from 70 to 80 per cent of cases. Within recent years surgical intervention has taken a secondary place in the treatment, which now consists largely in the use of the sulfonamide drugs and penicillin. The sulfonamide compounds had already reduced the mortality to between 50 and 30 per cent. An extensive bibliography is appended.

S. B. MARLOW

### Physiology

#### STUDIES ON THE PHYSIOLOGY OF THE EYE USING TRACER SUBSTANCES

I THE STEADY-STATE RATIO OF SODIUM BETWEEN PLASMA AND AQUEOUS HUMOR IN THE GUINEA PIG. R. O. SCHOLZ, D. B. COWIE and W. S. WILDE, *Am J Ophth* 30: 1513 (Dec) 1947

Scholz, Cowie and Wilde used radioactive sodium as a tracer to study the distribution of sodium between the plasma and the aqueous and between the aqueous and the lens in the guinea pig. The steady state ratio—the sodium plasma-sodium aqueous ratio—was found to be 0.920.

W. S. REESE

### Physiology

#### STUDIES ON THE PHYSIOLOGY OF THE EYE USING TRACER SUBSTANCES

II THE TURNOVER RATE OF SODIUM IN AQUEOUS HUMOR OF THE GUINEA PIG. W. S. WILDE, R. O. SCHOLZ and D. B. COWIE, *Am J Ophth* 30: 1516 (Dec) 1947

Wilde, Scholz and Cowie compare the direct, or linear, method with the exponential method of calculating from tracer data the turn-over rate of a constituent in the aqueous humor of the eye. They find that the exponential method is the more accurate.

W. S. REESE

#### STUDIES ON THE OUTFLOW PRESSURE OF AQUEOUS IN HUMAN BEINGS

H. GOLDMAN, *Ophthalmologica* 114: 81 (Aug) 1947

The difference between the intraocular pressure and the pressure in the episcleral veins is the outflow pressure of the aqueous humor. This determines the rate of flow of the aqueous humor out of the eye. The author has sought to measure this outflow pressure by determining the pressure of the special spring balance put on the middle of the cornea which is just able to broaden the aqueous thread in a laminated episcleral vein, that is, in one of the aqueous veins visible in the conjunctiva and episclera. This pressure he calls the "apparent outflow pressure," and it is always increased during high pressure in a case of glaucoma. This apparent outflow pressure is increased in simple glaucoma, even if the tension of the eye has been rendered normal by drugs. On the other hand, in cases of acute glaucoma in which the pressure is normalized by drugs, this outflow pressure is normal. In cases of chronic congestive glaucoma in which the tension is normalized by drugs, it is sometimes found elevated and sometimes normal. Goldman believes that in 90 per cent of persons one can see the aqueous veins. Therefore, it seems possible to find out very early states of simple glaucoma by a rapid procedure, namely, the measurement of the apparent outflow pressure.

F. H. ADLER

### Refraction and Accommodation

THE SODIUM-VAPOR LAMP AND ITS USE FOR REFRACTION S VAN WIEN, *Am J Ophth* 30:1527 (Dec) 1947

Van Wien enumerates the advantages of sodium light for funduscopy, but he found no essential difference between it and polychromatic light in retinoscopy, nor did it improve visual acuity. With cycloplegia, print could be read at closer distance with white light, and this may be additional proof for so-called paradoxical accommodation.

W S REESE

EFFECT OF VISUAL TRAINING ON EXISTING MYOPIA H R HILDRETH, W H MEINBERG, B MILDRE, L T POST and T E SANDERS, *Am J Ophth* 30:1563 (Dec) 1947

The authors conclude that training improves the vision of some myopic persons, although there is no change in the refractive error. A recheck after an interval of fifteen to twenty-three months showed that 5 of 11 of the patients in their series retained the improvement.

W S REESE

### Retina and Optic Nerve

TREATMENT OF RETINITIS PIGMENTOSA WITH SPECIAL REFERENCE TO THE FILATOV METHOD D M GORDON, *Am J Ophth* 30:565 (May) 1947

Gordon reviews the various measures used in treatment of retinitis pigmentosa, giving attention to the Filatov method of tissue therapy. Work done at the New York Hospital with this method is presented as a guide to other investigators.

W S REESE

EPIDEMIC RETROBULBAR NEURITIS IN THE PHILIPPINES DURING THE JAPANESE OCCUPATION G DEOCAMPO, C V YAMBAO, P J MAÑAGAS and C L SEVILLA, *Am J Ophth* 30:698 (June) 1947

Data are given on 38 cases of retrobulbar neuritis, 2 of which are cited in detail as typical. The diagnosis and treatment are discussed. Predisposing factors are thought to be (1) individual and racial weaknesses of the nervous system, or "soil", (2) emotional strain of the war, and (3) focal infection, indulgence in tobacco and alcohol, lactation and other conditions.

W S REESE

RETINITIS PROLIFERANS AND TUBERCULOSIS G GIMENEZ RUIZ, *Arch Soc oftal hispano-am* 7:226 (March) 1947

Gimenez Ruiz presents 2 cases of proliferating retinitis in patients with tuberculosis. He assumes that the latter was the causative factor. One of the patients, a man aged 28, with active pulmonary tuberculosis, had current hemorrhages in the vitreous, and from these retinitis proliferans developed. The other patient, a man aged 23, showed increased density and areas of calcification in both pulmonary hiluses and chronically enlarged cervical lymph nodes. He also had repeated hemorrhages into the vitreous, which later became organized.

The author contends that preretinal hemorrhages must occur in order that retinitis proliferans may develop. The hemorrhages are preceded by phlebitis of the retinal veins, usually of tuberculous nature.

H. F. CARRASQUILLO

RETINAL PERIPHLEBITIS G. CARDILLO, *Rassegna ital. d'ottal.* 13:56, 1946

The author describes a case in which lesions of the fundus typical of periphlebitis were followed by severe retinal hemorrhage, without involving the vitreous, and a completely benign course, with conservation of visual function. The changes were only in the periphery of the fundus. In discussing the etiology, the author ruled out thromboangitis obliterans, focus of infection in the tonsils and hemorrhagic diathesis, and demonstrated its tuberculous nature by a strongly positive reaction to the intradermal test with tuberculin, by the constitutional habitus of the patient and by the regression of the perivenous exudates and the appearance of less serious hemorrhages after the intradermal reaction to tuberculin. The infection seems to be hematogenous. A cure with tuberculin could not be attained, but treatment with calcium, arsenic and ascorbic acid showed favorable response when autohemotherapy was added at the height of the hemorrhagic episodes.

G. B. BIETTI—J. J. LO PRESTI

### Trachoma

ELECTROMETRIC VARIATIONS IN THE TISSUE  $p_H$  IN TRACHOMA P. VANCEA, *Arch. d'opht.* 7:156, 1947

The author presents evidence indicating that the trachoma virus produces an increased acidity of the conjunctival tissues and that this acidity returns to normal as soon as the trachomatous foci are thrown off. The clinical cure is preceded by a reestablishment of the acid-base equilibrium, a reestablishment which can be considered a true biochemical cure and which is evident early as compared with the clinical condition.

S. B. MARLOW

### Tumors

PIGMENTED TUMORS A. B. REESE, *Am. J. Ophth.* 30:537 (May) 1947.

Reese, in this de Schweinitz Lecture, discusses tumors which seem to differ genetically, histologically and clinically but have one factor in common, namely, pigment. This tends to dominate the histologic and clinical picture and overshadows or excludes other fundamental differences. Therefore he suggests that the term "melanoma" be discarded, and he offers alternative designations.

W. S. REESE

NEUROBLASTOMA OF THE ADRENAL WITH ORBITAL METASTASES R. N. SHAFFER, *Am. J. Ophth.* 30:733 (June) 1947

Shaffer reports 5 cases of neuroblastoma of the Hutchinson type with autopsy observations. He emphasizes the importance of roentgenologic evidence of calcification above the kidney as a diagnostic aid. Radioactive phosphorus has been unsuccessful in the treatment of these patients.

W. S. REESE



LYMPHOCYTOMA OF THE ORBIT SUCCESSFULLY TREATED BY ROENTGEN  
IRRADIATION S VAN WIEN, *Am J Ophth* 31:209 (Feb) 1948

Van Wien presents a case of lymphocytoma of the orbit. The diagnosis was established by means of biopsy, and satisfactory response to roentgen therapy was obtained.

W S REESE

ORIGIN OF THE MALIGNANT MELANOMATA E WOLFF, *Brit J Ophth*  
33:72 (Feb) 1948

Wolff is opposed to the theory of a unitary origin of malignant melanoma. He believes that the nevus should be regarded as a composite, or mixed, tumor, consisting for the present purpose of nevus cells, epithelial cells and branched chromatophores. Each of these elements may proliferate alone or with the others to produce a malignant pigmented tumor. The final structure will depend on the relative proportions of the three types of cell.

W ZENTMAYER

### Uvea

RELATION OF ALLERGY TO ACUTE IRITIS P LEMOINE, *Arch d'ophth*  
7. 161, 1947

In recent years many authors have been inclined to attribute to allergy ocular conditions of uncertain cause which apparently are not due to a infectious process. The author summarizes three theories. The first is that of the liberation of histamine and the use of antihistamine drugs. The second theory is that of an antigen-antibody reaction, producing a flocculation of colloids, which, in turn, leads to vascular disturbances and to imbalance in control of the sympathetic nervous system. Magnesium hyposulfite has been used to prevent this process. A third theory incriminates the vascular endothelium. The author used magnesium hyposulfite in a series of 30 cases of acute iritis. These cases were divided into two groups: those in which regular injections were given and those in which the injection was difficult. In 8 of the 10 cases in the first group improvement was much more rapid than in the second group. The technic of the injections is given. A daily intravenous injection of 10 cm. of a 10 per cent solution of the drug is used for the first five or six days. The injections are then spaced according to the progress of the condition. The author cites 3 significant cases in which improvement was definitely more rapid. It was surprising that the antiallergic treatment was favorable in 25 of 30 cases, and the first case was especially interesting in that there seemed to be a close relation between the iritis and an intestinal disturbance. The author expresses the belief that the allergic hypothesis does not contraindicate the use of an etiologic medication. Hyposulfite intervenes only to check whatever allergic consequences may be present. In the majority of cases both types of treatment should be employed concurrently in order to obtain the maximum benefit to the patient.

S B MARLOW

### Vision

BINOCULAR VISION D CAMPBELL, *Brit J Ophth* 31:321 (June)  
1947

In this paper the Middlemore Lecture, Campbell reviews and analyzes the literature. As the common disorders of binocular vision, she

gives primary amblyopia and the allied condition of suppression, strabismus, both paralytic and concomitant, and heterophoria

The factors contributing to maintenance of perfect binocular vision in man are the overlapping of the visual fields, a strongly developed sense of fusion and the dominance of macular over peripheral vision. The maintenance of perfect binocular vision must depend on a bilateral harmony within the central area of the two mechanisms of pattern vision and fusion

The author has found that good binocular vision persists in the dark-adapted eye, even when the illumination of the test object is so low as to favor rod, rather than cone, vision. The author has arrived at the same conclusion as Verhoeff, that binocular vision depends on some form of physiologic replacement

Occlusion should not be left, as it so often is in the case of the hospitalized child, until the age of 5. It can be employed much earlier, or perhaps a better method is the use of atropine drops in the good eye

W ZENTMAYER

### Vitreous

OPERATIVE TECHNIC OF VITREOUS REPLACEMENT M H FRITZ T M FENNESSY and H CABRERA, *Am J Ophth* 30:1221 (Oct) 1947

This article describes the technic of replacement of vitreous with cerebrospinal fluid. This procedure was carried out on refrigerated human eyes. A plea is made for ophthalmologists to use this method in suitable cases

W S REESE

TRANSPLANTATION OF VITREOUS A PRELIMINARY REPORT H M KATZIN and J BLUM, *Brit J Ophth* 31:760, (Dec) 1947

A brief chronologic survey of the attempts made to remove vitreous without replacement or to replace it with saline solution, air or animal vitreous is given. The authors give the following summary of their experimental work. Transfer of vitreous was studied in 39 rabbit eyes, with a follow-up period of six months. Several types of procedure were used, these are described in the text, and a comparison of these procedures in the experimental animal and in the human eye is discussed

Traumatic cataract was produced in 2 cases, retinal detachments which persisted occurred in 6 cases, and localized proliferation of fibrous tissue around the site of puncture, in 7 cases. These complications, particularly the retinal detachment, are significant and should be borne in mind in the election of vitreous transfer as a clinical procedure

W ZENTMAYER

### Therapeutics

AN ATTEMPT TO TREAT A PERFORATED EYE WITH SUBCONJUNCTIVAL PENICILLIN F R NEUBERT, *Brit J Ophth* 32:162 (March) 1948

The eyeball had been perforated through the cornea by a wire. On the second day 50,000 units of penicillin in epinephrine and "nuvatox" was injected subconjunctivally and 30,000 units was given intramuscularly. This subconjunctival injection was repeated twice. On the

fifth day the eye was enucleated because of beginning panophthalmitis  
The diagnosis was confirmed pathologically

W ZENTMAYER

TISSUE THERAPY OF OCULAR COMPLICATIONS IN PATIENTS WITH  
HYPERTENSION D BUSHMITCH *Oftal zhui* 2 36, 1946

During the siege of Leningrad, in 1942, the oculists were the first to observe the increase of hypertension because of the frequency of angio-spastic retinitis among patients at the ophthalmic clinics

Twenty-four patients with hypertension accompanied with retinal changes, hemorrhages, neuroretinitis and atrophy of the optic nerve (4 patients) were treated with injections of autoclaved preserved leaves of aloe combined with implantations of preserved skin of the cadaver. In all patients improvement in the general condition (in 11, the blood pressure was lowered) and in the fundus picture was observed, most of the retinal hemorrhages were absorbed, the edema of the disk decreased, and in the majority vision improved. The headaches disappeared in several cases. The effect of the treatment was not permanent, and the injections had to be repeated in two to three months. The treatment was given ambulatory patients

O SITCHEVSKA

TISSUE THERAPY OF TRAUMATIC CHANGES OF THE VITREOUS IN THE  
PERIOD OF WORLD WAR II I ERSHKOVICH, *Vestnik oftal* 25 16, 1946

The statistical data of World War II indicate that hemorrhages into the vitreous occur in from 17 to 58 per cent of all cases of ocular injury. Ershkovich analyzes the various end results of hemorrhage in the vitreous and the various methods of treatment applied by the Soviet ophthalmologists.

He used tissue therapy in 20 cases of opacities in the vitreous resulting from war injuries in a military hospital. In 2 cases the injury was caused by a bullet, in the others, by fragments of mines and grenades. In 14 cases there was a penetrating injury, and in 6, contusion of the eyeball. In all cases there were severe complications from the injury: intraocular foreign bodies, 6 cases, retinal detachment, 7 cases, and proliferative retinitis, 2 cases. In 3 cases the remaining eye was affected, the other eye having been enucleated at the front.

Tissue therapy was applied from one to nine months after the injury. In 10 cases it was combined with osmotherapy, and in the other 10 cases it was used alone. Implantation of preserved placenta beneath the skin of the ear or under the conjunctiva, intramuscular injections of cod liver oil, and subcutaneous injections of preserved blood were used. In 17 cases repeated courses of tissue therapy were employed. The time of observation was from three months to two and one-half years.

Tissue therapy gave improvement in 18 cases, including those of intraocular foreign bodies and detachment of the retina. Vision was improved in many cases from light projection and counting fingers to 0.05, 0.1 or 0.4.

Ershkovich urges the use of tissue therapy in traumatic changes of the vitreous, even in apparently hopeless cases.

OLGA SITCHEVSKA

## Book Reviews

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**Oculus: Tabulae Biologicae. Volume 32, Part I** Edited by K Steindorff, F P Fischer, J S Friedenwald and Arnold Sorsby Price, 60 florins Pp 408 Amsterdam Netherlands, Uitgeverij W Junk, 1947

The thirteenth volume of the "Tabulae Biologicae," which is devoted to the eye, has been planned for publication in four parts. The first part has now appeared in print, about ten years after work on this great undertaking was initiated. Morphologic data are presented in the chapters on the eye of the invertebrates, by H Kahmann, the metric and descriptive characteristics of the human and the animal eye, by St Martin-Oppenheim, and the descriptive anatomy of the vertebrate and the human eye, by K Steindorff, as well as in the brief section on the embryology of the vertebrate eye, by C Dejean and F Granel. In the three additional divisions, J Nordmann discusses the anatomic, physiologic and pharmacologic aspects, and K W Ascher, intraocular pressure and blood pressure in the ocular vessels.

The descriptive and comparative anatomic material is almost exclusively presented in the form of tables, without connecting or explanatory text except for the condensed treatise on embryology. The amount of information embodied in the tables is overwhelming. It is collected from widespread sources, and as a presentation of facts nothing on the oculist's bookshelf is comparable to it. A good, although not complete, list of references pertaining to the tabulated data is appended to each section. This will enable the reader to judge the statistical value or significance of the findings and measurements tabulated by returning to the original papers. In the chapters concerned with the embryologic, physiologic and pharmacologic phases, the subject matter is described with a minimum of words, without discussion or comment. The authors obviously adhere to the primary purpose of the work, namely, to convey facts, not theories.

The ophthalmologist will be attracted first by the instructive and exhaustive section on anatomy, by Steindorff, and by the sections on intraocular pressure and blood pressure in the ocular vessels, by Ascher. It is true that none of these sections is complete or brought up to date, as the literature published after 1937 either is not or is insufficiently covered, but this disadvantage is compensated for by a concise presentation of a stupendous mass of measurements and results in the various phases of ocular anatomy and physiology.

Not only will this monumental piece of work serve as a book for reference in biologic libraries and research laboratories, but the facts which it offers will often provide satisfactory answers to questions occurring in investigative work. It will be necessary to make the abundance of information in this book readily accessible by a good index. In fact, the completeness of such an index will determine the practical value of the book.

LUDWIG VON SALLMANN, M D

**Ophthalmology in the War Years Volume 2 (1944—June 1946).**

Edited by Meyer Wiener, MD Price, \$16 Pp 977 Chicago  
The Year Book Publishers, Inc, 1948

With the appearance of the second volume, ophthalmologic literature during the war years has now been completely covered. Owing to the difficulty in obtaining scientific articles and books during the war years, ophthalmologists will value the completion of this series and add the expression of their thanks to Dr Wiener and to his admirable group of associate editors. The labor and painstaking diligence which the collection of the titles and the writing of the review articles must have taken testify to the altruism and devotion of the editors. New chapters have been added and some omissions in the first volume, reviewed in the ARCHIVES (37: 258 [Feb] 1947) have been corrected.

The subjects and their authors are as follows: "Anatomy and Embryology," John J Prendergast, "Biochemistry, Pharmacology and Toxicology," W. Mouton Grant and David G Cogan, "Chemical Warfare Agents Effects on the Eye and Their Treatment," Jonas S Friedenwald and William F Hughes Jr, "Color Deficiency," Louise L Sloan, "Comparative Ophthalmology," Helenor Campbell Wilder, "Congenital Anomalies," Arthur M Yudkin, "Conjunctiva," Edward P Burch, "Cornea and Sclera," Ramon Castroviejo, "Corneal Epithelium Mitosis and Wound Healing," Jonas S Friedenwald, "Electrophysiology," S Howard Bartley, "Experimental Pathology" Peter C Kronfeld, "General Pathology and Bacteriology," S Rodman Irvine and Mary Dailey Irvine, "Glaucoma," Otto Barkan, "Hygiene, Sociology, Education and History," Windsor S Davies, "Industrial Ophthalmology," Hedwig S Kuhn, "Injuries," Robert J Masters, "The Lens," Ray K Daily and Louis Daily Jr, "Lids and Lacrimal Apparatus," Harold F Whalman, "Methods of Examination," Leo L Mayer, "Neuro-Ophthalmology," P J Leinfelder, "Ocular Neuromotor Mechanism," George P Guibor, "Orbit, Eyeball and Sinuses," William L Benedict, "Physiologic Optics," Kenneth N Ogle, "The Pupil," Henry Minsky, "Refraction and Accommodation," E Merle Taylor, "Relationship of the Eye to the Nose and Throat," W Nicholas Sauer, "Retina and Vitreous," Hugo Lucic, "Surgery of the Eye," Bennett Y Alvis and Edmund B Alvis, "Systemic Diseases, Syphilis, Parasites," Joseph Igersheimer, "Therapeutics," Frederick C Cordes, "Trachoma," Phillips Thygeson, "Tumors," Jack S Guyton, and "Uveal Tract," William M James.

A brief study of the text will convince the reader of the excellence of the reviews and the completeness of the subjects listed. Again, our thanks to Dr Wiener and his associates for this admirable volume.

ARNOLD KNAPP

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All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6<sup>e</sup>, France

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Brazil (South of Panama)  
Place Mexico City Time 1952

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\* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date

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 Place The Buena Vista Hotel, Biloxi, Miss Time May 9, 1949

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 second Thursday in October, December, February and April

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 Akron 8, Ohio  
 Place Akron City Club Time 6 30 p m, first Monday in January, March,  
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 Secretary Dr James T King, Medical Arts Bldg, Atlanta, Ga  
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 from October to May.

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 Secretary Dr James I Moore, 11 E Chase St, Baltimore  
 Place Medical and Chirurgical Faculty, 1211 Cathedral St Time 8 30 p m,  
 fourth Thursday of each month from October to March

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 September to May, inclusive

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 Secretary-Treasurer Dr Louis Freimark, 256 Rochester Ave, Brooklyn 13  
 Place Towers Hotel, 25 Clark St Time 8 15 p m, third Thursday in February,  
 April, October and December

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 Secretary-Treasurer Dr Herbert R Reitz, 446 Linwood Ave, Buffalo 9  
 Place Park Lane Time Second Thursday of each month from October  
 to May

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Place Illini Union Bldg Time 7 30 p m third Monday of each month from October to May

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Place Cincinnati General Hospital Time 8 00 p m, second Friday of each month from November to May, inclusive

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Secretary Dr Roscoe J Kennedy, 2020 E 93d St, Cleveland 6

Place Hotel Statler, Cleveland Time Second Tuesday in November, January, February and April

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Clerk Dr M Luther Kauffman, Medical Arts Bldg, Jenkintown, Pa

Place College of Physicians Bldg Time 8 15 p m, third Thursday of every month from October to May, inclusive

## COLUMBUS EYE, EAR, NOSE AND THROAT SOCIETY

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Secretary-Treasurer Dr W J Miller, 21 E State St, Columbus, Ohio

Place University Club Time 6 00 p m, first Monday of each month, from October to May, inclusive

## CORPUS CHRISTI EYE, EAR, NOSE AND THROAT SOCIETY

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Secretary Dr B B Friedman, Jones Bldg, Corpus Christi, Texas

Place Nueces Hotel Time 6 30 p m, third Tuesday of each month from October to May

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Secretary Dr C A Hoefler, 1719 Pacific Ave, Dallas 1, Texas

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 Secretary-Treasurer Dr H H Grau, 213 Bankers Trust Bldg, Des Moines, Iowa  
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 Place Club rooms of Wayne County Medical Society Time Third Thursday of each month, November to April, inclusive

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 Secretary Dr William S Gonne, 619 David Whitney Bldg, Detroit 26  
 Place Hayler's L'Aiglon Bldg Time 6 30 p m, third Thursday of each month from November to April, inclusive

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 Secretary-Treasurer Dr E Martin Freund, 762 Madison Ave, Albany 3  
 Place Albany, Troy, Schenectady, rotating monthly Time First Thursday of every month

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 Place All Saints Hospital Time 6 30 p m, first Friday of each month except July and August

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 Secretary Dr R Marion Johnson, Medical Arts Bldg, Houston Texas  
 Place River Oaks Country Club Time 6 30 p m, second Thursday of each month from October to June

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 Secretary Dr J Lawrence Sims, 23 E Ohio St, Indianapolis  
 Place Indianapolis Athletic Club Time 6 30 p m, second Thursday of each month from November to May

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 Secretary-Treasurer Dr Orville W Cole, 305 Professional Bldg Long Beach 2, Calif  
 Place Seaside Hospital Time 6 15 p m third Wednesday of each month from October to May



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 Secretary Dr John A Bullis, 3875 Wilshire Blvd, Los Angeles 5  
 Place 3550 Wilshire Blvd, Los Angeles Time 6 30 p m, third Tuesday of each month, September through June

## LOS ANGELES SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Secretary-Treasurer Dr Warren A Wilson, 1930 Wilshire Blvd, Los Angeles 5  
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OPHTHALMOLOGY AND OTOLARYNGOLOGY

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 Place 1718 M St N W Time 8 p m, third Friday of each month from October to April, inclusive

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 Secretary Dr Sam H Sanders, 1089 Madison Ave., Memphis, Tenn  
 Place Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital Time 8 p m, second Tuesday of each month from September to May

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 Secretary-Treasurer Dr George O Dunker, 208 E Wisconsin Ave, Milwaukee  
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 Secretary-Treasurer Dr Matland D Place, 981 Reibold Bldg, Dayton, Ohio  
 Place Van Cleve Hotel Time 6 30 p m, first Tuesday of each month from October to June, inclusive

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 Secretary Dr R Cloutier, 3445 Papineau Ave, Montreal, Canada  
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 Secretary Dr N B Norris, Doctors Bldg, Nashville 3, Tenn  
 Place James Robertson Hotel Time 6 30 p m, third Monday of each month from October to May

NEW ORLEANS OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETY

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 Secretary Dr Mercer G Lynch, Ochsner Clinic, New Orleans  
 Place Charity Hospital Time 8 p m, first Tuesday of every month

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 Secretary D<sub>1</sub> Isadore Givner, 108 E 66th St, New York 21  
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 Secretary Dr Leon Ehrlich, 211 Central Park W, New York  
 Place New York Academy of Medicine, 2 E 103d St Time 8 p m, first Monday  
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President Dr William Mussil, Medical Arts Bldg, Oklahoma City  
 Secretary Dr Charles A Royer, 717 Medical Arts Bldg, Oklahoma City  
 Place University Hospital Time 7 30 p m, first Tuesday of each month  
 from September to June

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 Secretary-Treasurer Dr W Howard Morrison, 1500 Medical Arts Bldg, Omaha 2  
 Place Omaha Club, 20th and Douglas Sts, Omaha Time 6 p m dinner, 7 p m  
 program, third Wednesday of each month from October through April

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 Secretary-Treasurer Dr J Averbach, 435 Clifton Ave, Clifton, N J  
 Place Doctors Lounge, Paulsen Medical and Dental Bldg Time 8 p m, last  
 Tuesday of each month except June, July and August

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 Secretary Dr Robert T M Donnelly, 255 S 17th St, Philadelphia  
 Time First Thursday of each month from October to May

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 Secretary Dr Samuel D Evans, Park Bldg, Pittsburgh 22  
 Place Pittsburgh Academy of Medicine Bldg Time 8 00 p m, fourth Monday  
 of each month, except June, July, August and September

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 Secretary Dr Paul C Craig, 232 N 5th St, Reading, Pa  
 Place Wyomissing Club Time 6 00 p m, third Wednesday of each month  
 from September to July

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 Secretary Dr George N Thrift, Medical Arts Bldg, Richmond, Va  
 Place Commonwealth Club Time 6 p m, first Tuesday of January, March  
 May and October

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 Secretary Dr J H Bryan, 327 Beaumont Bldg, St Louis 8  
 Place Elliott Auditorium, McMillan Hospital Time Fourth Friday of each month from October to April inclusive, except December, at 8 00 p m

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 Place San Antonio, Texas, Brooke General Hospital and Randolph Field Time 7 p m, second Tuesday of each month from October to May

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 Secretary Dr William Duggan, 490 Post St, San Francisco 2  
 Place Society's Bldg, 2180 Washington St, San Francisco 9 Time 8 15 p m, fourth Tuesday of every month except June, July and December

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 Secretary-Treasurer Dr Frank L Bryant, 2622 Greenwood Rd, Shreveport 2 La  
 Place Shreveport Club Time 6 30 p m, first Monday of every month except June, July and August

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 Secretary Dr Raymond A Lower, Paulsen Medical and Dental Bldg, Spokane Wash  
 Place Library, Paulsen Medical and Dental Bldg Time 8 p m fourth Tuesday of each month except June, July and August

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 Secretary Dr Thomas A Egan, 1835 Eye St N W, Washington, D C  
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 Secretary Dr Samuel T Buckman, 70 S Franklin St, Wilkes-Barre, Pa  
 Place Luzerne County Medical Society Time 1st Tuesday of each month from October to May

## ROLE OF INHERITANCE IN GLAUCOMA

ADOLPH POSNER, M D

AND

ABRAHAM SCHLOSSMAN, M D

NEW YORK

HEREDITY is often stressed as an important factor in the pathogenesis of glaucoma. Yet, to date, only approximately 90 pedigrees of families with glaucoma have been reported in the literature. Since these family trees are presented as isolated examples, without relation to glaucoma as a whole, they create the impression that hereditary glaucoma is rare and that it is different from the nonhereditary form.

In the course of a study of 373 cases of primary glaucoma, we were impressed by the high incidence of patients displaying familial tendencies. Fifty-one patients had one or more relatives affected with the disease. As early as 1880, Schenkl<sup>1</sup> stated that there is hardly an ophthalmologist who has not met with several hereditary cases. In fact, many patients demonstrate their awareness of the hereditary possibilities of the disease by the questions they put to the ophthalmologist. There is obviously a discrepancy between the paucity of the material in the literature and the everyday experience of the physician. A new approach is needed to the study of the role of inheritance in glaucoma, especially in the light of the more recent advances in genetics. While this paper represents a limited experience, it is hoped that the pooling of similar studies will supply enough data for a more adequate investigation of this genetic problem.

Correlations made in the preparation of this survey suggested the possibility of using the hereditary group as a starting point for the investigation of some of the more elusive problems in glaucoma, such as (1) the preglaucomatous state, (2) the possibility of predicting the probable severity of the disease and (3) the relation between glaucoma and certain constitutional diseases.

Recently, emphasis has been placed on the early recognition of glaucoma. Lowenstein and Schoenberg<sup>2</sup> studied the apparently unaffected

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Presented in part at the Fifty-Second Annual Meeting of the American Academy of Ophthalmology and Otolaryngology, Chicago, Oct 15, 1947.

<sup>1</sup> Schenkl. On the Heredity of Glaucoma, *Prag med Wchnschr* 5:413-414, 1880.

<sup>2</sup> Lowenstein, O., and Schoenberg, M. J. Pupillary Reactions of the Seemingly Unaffected Eye in Clinically Unilateral Simple Glaucoma, *Arch Ophth* 31:392-398 (May) 1944.

eye in cases of monocular glaucoma by means of pupillography and found that the pupillary reactions were similar in the two eyes. Bloomfield and Lambert<sup>3</sup> used the lability test as an aid to early diagnosis. Downey<sup>4</sup> emphasized the importance of differences in tension between the two eyes as indicating a tendency toward glaucoma. Moreu<sup>5</sup> attempted to investigate the preglaucomatous state by correlating the various clinical findings.

The term "preglaucoma" was introduced by Gradle<sup>6</sup> in 1924. As used by him, however, it refers to glaucoma in a mild or early stage. It should be emphasized that "preglaucoma" must be differentiated from the preclinical stage, in which the eye is clinically normal. In order to gain insight into the preclinical stage, one is obliged to study normal persons.

Since the incidence of glaucoma in the general population is at most 0.5 to 2 per cent, it is obviously impossible to subject a random sample of normal persons to any series of clinical tests in the hope of shedding light on the preclinical stage. It would seem more advisable to use the families of patients with glaucoma. Schoenberg<sup>7</sup> reported on the results of the use of the Knapp epinephrine test in the brothers, sisters and children of patients with glaucoma. The hereditary group is particularly suited to such a study because it represents a sample with a high incidence of glaucoma and because of the mathematical probability that some members who are normal at present will ultimately have the disease.

To the patient and to his family, it is of the utmost importance to know whether his disease will follow a mild course or will lead to blindness. In fact, too little emphasis has been placed on this vital question, which is discussed elsewhere in greater detail.<sup>8</sup> The genetic approach is helpful in predicting the probable course in a case of glaucoma.

In taking careful pedigrees in routine cases of glaucoma, we have noted a high incidence of certain metabolic and regulatory diseases, such as diabetes, hypertensive vascular disease and obesity, among the unaffected members of the family. It is possible that there exists

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3 Bloomfield, S., and Lambert, R. K. The Lability of Ocular Tension, *Arch Ophth* **34** 83-94 (Aug) 1945.

4 Downey, H. R. Unequal Tension as a Sign in Early Glaucoma, *Tr Am Ophth Soc* **43** 495-504, 1945.

5 Moreu, A. El problema del glaucoma verum, Buenos Aires, Salvat Editores, 1946, pp 103-139.

6 Gradle, H. S. Preglaucoma, *Am J Ophth* **29** 520-523, 1946.

7 Schoenberg, M. J. The Knapp Adrenalin Mydriasis Reaction in Direct Descendants of Patients with Primary Glaucoma, *Tr Am Ophth Soc* **22** 53-59, 1924.

8 Posner, A., and Schlossman, A. Mild Glaucoma, *Am J Ophth* **31** 679 (June) 1948.

a genetic relation among all these diseases.<sup>9</sup> This problem is a difficult one, and, in view of the fact that we became aware of these possibilities while the present study was in progress, it was impossible to collect sufficient data to permit us to arrive at any definite conclusions.

#### REVIEW OF LITERATURE

Since the cases reported in the literature are not representative of the total experience with glaucoma, no definite information is available as to the relative incidence of cases showing familial tendencies. Only Biró<sup>10</sup> has attempted to estimate the incidence of hereditary cases among the patients with glaucoma in his clinic. Of 761 patients, 43 had a familial history of the disease. They belonged to 36 families and comprised 5.6 per cent of the total series.

Benedict,<sup>11</sup> in 1842, was, so far as we know, the first to call attention to the familial tendencies of the disease. He reported glaucoma in two dark-eyed daughters of an extremely gouty old general. Arlt<sup>12</sup> sketchily described 3 families in 1860, and Bowman<sup>13</sup> added another family tree in 1865. The latter referred to glaucoma as the "most subtle of the hereditary affections of the eye." In 1869, however, von Graefe,<sup>14</sup> while he did not report any pedigrees, stated that he had seen many cases with familial tendencies. He discussed certain observations regarding the nature of hereditary glaucoma. He stated that in many cases there were long prodromal periods, ranging from eight to sixteen years. In 1 case a mother and daughter were stricken with glaucoma in the same year, although there was an age difference of 26 years between the two. This and other cases led him to formulate the concept of anticipation, or the tendency for the disease to appear at an earlier age in succeeding generations. He also reported that noncongestive glaucoma was far less frequent among the hereditary cases than was inflammatory glaucoma. Glees and Ried,<sup>15</sup> on the other hand, stated that the chronic simple form is more commonly familial.

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9 Lowenstein, O. Personal communication to the authors.

10 Biró, I. Primary Glaucoma. Notes on the Heredity of Glaucoma, *Ophthalmologica* **98** 43-50, 1939.

11 Benedict, T. W. G. *Abhandlungen aus dem Gebiete der Augenheilkunde*, Breslau, 1842, pp 123-132.

12 von Arlt, C. G. *Die Krankheiten des Auges für praktische Ärzte*, Prague, F. A. Credner, 1860, vol 2, pp 190-209.

13 Bowman, W. *Ophthalmic Miscellanies*, *Ophth Hosp Rep*, London **5** 1-15, 1866.

14 von Graefe, A. *Pathology and Treatment of Glaucoma*, *Ophth Hosp Rep*, London **7** 112, 1871-1873.

15 Glees, M., and Ried, A. Glaucoma in a Pedigree of Three Generations, *Arch f Ophth* **142** 495-502, 1940.

The pedigrees in the literature fall into three main groups (1) those in which all the affected members have juvenile glaucoma, (2) those in which, owing to anticipation, the parents or grandparents have adult glaucoma, while in the succeeding generations the affected members have juvenile glaucoma, (3) those in which all the affected members have adult glaucoma

The first two groups include some of the most carefully worked-out pedigrees Plocher<sup>16</sup> and Berg<sup>17</sup> traced glaucoma in six generations Harlan,<sup>18</sup> Courtney and Hill,<sup>19</sup> Stokes<sup>20</sup> and Glees and Ried<sup>15</sup> reported pedigrees in which the disease was present in five generations Several excellent family trees tracing glaucoma in young people through several generations were presented by Allmares,<sup>21</sup> Preobrazhenskiy,<sup>22</sup> Zorab,<sup>23</sup> Neamé,<sup>24</sup> Calhoun,<sup>25</sup> Howe,<sup>26</sup> Werner,<sup>27</sup> Kaufman,<sup>28</sup> Snell,<sup>29</sup> Biró<sup>10</sup> Allen and Ackerman<sup>30</sup> and Shumway<sup>31</sup>

In the third group there are few pedigrees which have been followed for even three generations This is due partly to the difficulty in following hereditary disease later in life and partly to the fact that some patients with potential glaucoma do not live long enough to reach the age at which they would have the disease From the relative preponderance of the reported pedigrees which are concerned with

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16 Plocher, R. Contribution to Juvenile Familial Glaucoma, *Klin Monatsbl f Augenh* **60** 592-620, 1918

17 Berg, F. Glaucoma in Young Persons, *Acta ophth* **10** 568-587, 1932

18 Harlan, H. A Case of Hereditary Glaucoma, *J A M A* **5** 285-286 (Sept 12) 1885

19 Courtney, R H, and Hill, E. Hereditary Juvenile Glaucoma Simplex, *Tr Sect Ophth, A M A*, 1931, pp 47-68

20 Stokes, W H. Primary Glaucoma Pedigree with Five Generations, *Arch Ophth* **24** 885-909 (Nov) 1940

21 Allmares, F. Familial Glaucoma in Two Generations, *Ztschr f Augenh* **95** 276-279, 1938

22 Preobrazhenskiy, V V. Hereditary Glaucoma in Young Persons, *Vestnik oftal* **16** 326-332, 1940

23 Zorab, A. Glaucoma Simplex Familiaris, *Tr Ophth Soc U Kingdom* **52** 446-460, 1932

24 Neamé, H, in discussion on Zorab<sup>23</sup>

25 Calhoun, F P. Hereditary Glaucoma Simplex, *J A M A* **63** 209-215 (July 18) 1914

26 Howe, L. A Family History of Blindness from Glaucoma, *Arch Ophth* **16** 72-76, 1887

27 Werner, S. Hereditary Juvenile Glaucoma Four Cases, *Acta ophth* **7** 162-168, 1929

28 Kaufmann, F. Statistics on the Heredity of Eye Diseases, *Wchnschr f Therap u Hyg des Auges* **9** 68-69, 1928

29 Snell, A C. Hereditary Glaucoma Simplex (Juvenile Glaucoma), *New York State J Med* **23** 151-154, 1923

30 Allen, T D, and Ackerman, W G. Hereditary Glaucoma in a Pedigree of Three Generations, *Arch Ophth* **27** 139-156 (Jan) 1942

31 Shumway, in discussion of Courtney and Hill<sup>19</sup>

juvenile glaucoma one forms the erroneous impression that juvenile glaucoma is the most commonly inherited form. In our experience, adult hereditary glaucoma is by far the commoner type. This is what one might expect, in view of the relative infrequency of juvenile glaucoma in general. Of the cases described in this paper, 5 belong to the juvenile and 45 to the adult type, none of our pedigrees show inheritance limited to the juvenile form.

Lawford<sup>32</sup> has treated the subject of inheritance of adult glaucoma more extensively than any other author. He described 5 family trees in which glaucoma came on after 40 years of age. All these patients had chronic simple glaucoma except 2, who had the acute congestive type.

Kirkpatrick<sup>33</sup> described a Jewish family in which 4 members, belonging to three generations, acquired glaucoma after the age of 40. Briggs<sup>34</sup> and James<sup>35</sup> published pedigrees which showed insidious onset of glaucoma in adults over 40. Other pedigrees have been described by Schenkl,<sup>1</sup> Jacobson,<sup>36</sup> Nettleship,<sup>37</sup> Rogman,<sup>38</sup> Usher,<sup>39</sup> Pagenstecher<sup>40</sup> and Holland.<sup>41</sup> Bartels<sup>42</sup> described "glaucoma climactericum" in a mother and 4 daughters.

The question arises whether there is any real difference between juvenile and adult glaucoma. This is extremely important for the study of heredity, for, if there were no essential difference, we should be able to pool certain pedigrees without regard to the age of onset.

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32 Lawford, J. B. Examples of Hereditary Glaucoma, *Roy London Ophth Hosp Rep* **17** 57-64, 1907-1908, Examples of Hereditary Glaucoma, *ibid* **19** 42-44, 1913-1914.

33 Kirkpatrick, cited by Bell, J., in Pearson, K. Anomalies and Diseases of the Eye, pt 5, Treasury of Human Inheritance, Eugenics Laboratory Memoirs XXVII, London, Cambridge University Press, 1926, vol 2, p 514.

34 Briggs, A. H. Familial Primary Glaucoma in Adults, *Brit J Ophth* **23** 649-59, 1939.

35 James, R. R. Pedigree of a Family Showing Hereditary Glaucoma, *Brit J Ophth* **2** 438-443, 1937.

36 Jacobson, J. Contributions to the Study of Glaucoma, *Arch f Ophth* **32** 96-168, 1886.

37 Nettleship, E. Some Hereditary Diseases of the Eye, *Ophthalmoscope* **4** 549, 1906.

38 Rogman, A. On the Pathogenesis of Chronic Glaucoma. A Glaucomatous Family, *Ann ocul* **5** 73-75, 1899.

39 Usher, C. H., cited by Bell, J., in Pearson, K. Anomalies and Diseases of the Eye, pt 5, Treasury of Human Inheritance, Eugenics Laboratory Memoirs XXVII, London, Cambridge University Press, 1926, vol 2, p 524.

40 Pagenstecher, H. A. Klinische Beobachtungen aus der Augenheilanstalt zu Wiesbaden, Wiesbaden, C. W. Kiredel, 1861.

41 Holland, H. I. Hereditary Glaucoma Affecting Three Generations, *Indian M Gaz* **59** 408, 1924.

42 Bartels, V. Chronic Hereditary Climacteric Glaucoma, *Ztschr f Augenh* **48** 298, 1922.



Most authors accept 35 years as the upper age limit for the onset of juvenile glaucoma. It is obvious that when an arbitrary age limit is set many cases must fall into this group for no other reason than that the disease is discovered before the patient has attained the age limit. Glaucoma may exist without symptoms for several years and thus may not be detected until a few years after its incipience. Moreover, chronologic age is not a sound criterion to follow in dealing with biologic processes. There is a fundamental weakness in the use of an arbitrary age limit in defining a disease, especially since the characteristics of the disease are not essentially different in the two age groups and since authorities differ as to the age limit.

Anderson<sup>43</sup> stated the belief that hydrophthalmos is the result of a structural defect early in life, while senile glaucoma is due to degenerative factors associated with the aging process. He placed juvenile glaucoma somewhere between these two types, and he assumed that both factors are pathogenetic in this intermediate group. Supporting this thesis from a hereditary point of view are 4 pedigrees reported by Lohlein,<sup>44</sup> Berg,<sup>17</sup> Strehler<sup>45</sup> and Korte,<sup>46</sup> respectively. In these pedigrees, hydrophthalmos occurred in the same family in which other members had juvenile or adult glaucoma. Franceschetti,<sup>47</sup> on the other hand, claimed that hydrophthalmos is transmitted as a recessive character.

According to Anderson,<sup>48</sup> 87 per cent of cases of hydrophthalmos are recognized before the end of the first year of life, while Lohlein's<sup>44</sup> figures show that 78.9 per cent of juvenile glaucoma appears between the ages of 15 and 30, with a peak of 38.8 per cent between the ages of 16 and 20. Haag,<sup>49</sup> on the other hand, showed a gradually increasing percentage of patients with glaucoma, starting with 0.4 per cent at the age of 1 to 10 years and rising to 31.9 per cent in the age group of 61 to 70 years. Of his cases of juvenile glaucoma, 61.2 per cent began at 26 to 35 years of age. This is in line with our own statistics on juvenile glaucoma. These figures lead to the conclusion that hydrophthalmos is purely congenital, while juvenile and adult glaucoma are distinct from hydrophthalmos and may be regarded as the same disease. It is possible that in a small proportion of cases juvenile glaucoma may be related to hydrophthalmos.

43 Anderson, J. R. *Hydrophthalmia or Congenital Glaucoma*, London, Cambridge University Press, 1939, p. 8.

44 Lohlein, W. *Juvenile Glaucoma*, *Arch f Ophth* **85** 393-488, 1913.

45 Strehler, cited by Korte.<sup>46</sup>

46 Korte, W. *Contribution to the Heredity of Glaucoma*, *Klin Monatsbl f Augenh* **102** 664-668, 1939.

47 Franceschetti, A., in Schieck, F., and Brückner, A. *Kurzes Handbuch der Ophthalmologie*, Berlin, Julius Springer, 1930, vol. 1, pp. 713-714.

48 Anderson,<sup>48</sup> pp. 5-16.

49 Haag, C. *Juvenile Glaucoma*, *Klin Monatsbl f Augenh* **54** 133-167, 1915.

The incidence of cases of hereditary glaucoma in the age groups below 35 years has been estimated to be 18 (Keerl<sup>50</sup>) and 20 per cent (Lohlein<sup>44</sup>) of all cases of glaucoma

One argument which is frequently offered to prove that juvenile glaucoma is distinct from adult glaucoma is the preponderance of myopia in the younger group. Lohlein gave the incidence of myopia in cases of juvenile glaucoma as 50 per cent. In Plocher's pedigree, which is often cited as corroborating evidence, there were 17 cases of myopia. In most of these cases the degree of myopia was  $-1.00$  D or less and in only 4 was the myopia over 3 D. Our series of patients with glaucoma of all ages shows an incidence of 18 per cent myopia.<sup>51</sup> It is possible to account for some of the cases of myopia in the juvenile group by assuming that the increased tension results in a stretching of the young eye. An alternative view was held by von Graefe,<sup>14</sup> who stated the belief that myopia and glaucoma show similar mechanisms of inheritance. Our statistics do not show a greater incidence of myopia among the cases of juvenile glaucoma than in the over-all series. We have 5 cases of myopia above  $-0.5$  D among 23 patients whose glaucoma began earlier than 35 years of age.

Since there is no fundamental difference between juvenile and adult glaucoma in the signs, symptoms and course of the disease, we may group them together in our study of heredity.

Glaucoma is said to be more prevalent among persons of certain races. Jews and Negroes are thought to be more susceptible. Hereditary glaucoma has been reported from all parts of the world. Dérier<sup>52</sup> described a pedigree in Czechoslovakia. Ibrahim<sup>53</sup> published 2 pedigrees from Egypt, and Holland<sup>41</sup> reported 2 from India. Rampoldi<sup>54</sup> and Cassini<sup>55</sup> described several cases in Italy. Preobrazhenskiy<sup>22</sup> and Makarov<sup>56</sup> reported pedigrees from Russia. Waardenburg<sup>57</sup> described

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50 Keerl, M. Juvenile Glaucoma, Inaug. Dissert., Leipzig, Emil Lehmann, 1920.

51 Posner, A., and Schlossman, A. The Clinical Course of Glaucoma. A Review of 474 Cases from Private Practice, *Am J Ophth* **31**:915 (Aug.) 1948.

52 Dérier, J. Juvenile Glaucoma, *Bratisl. lékař. listy* **10** 600-602, 1930.

53 Ibrahim, F. G. Two Glaucomatous Families, *Bull. Ophth. Soc. Egypt* **34** 28-30, 1941.

54 Rampoldi, R. Due note voli osservazioni di glaucoma, *Ann. di ottal.* **13**: 347-351, 1884.

55 Cassini, F. Simple Chronic Glaucoma in Eight Members of Family, *Arch. ottal.* **47** 1-15, 1940.

56 Makarov, N. Y. Peculiar Hereditary Form of Idiopathic Glaucoma in Transbaikalia, *Vestnik oftal.* **10** 850-855, 1937.

57 Waardenburg, P. J. Das menschliche Auge und seine Erbanlagen, The Hague, M. Nijhoff, 1932, pp. 327-343, Observations on the Heredity in Borderline Cases Between Juvenile and Senile Glaucoma, Also Between Infantile and Juvenile Glaucoma, *Arch. f. Ophth.* **140** 662-686, 1939.

a family tree in Netherlands. Examples are available in the American, French,<sup>58</sup> Scandinavian and German literatures.

Various hypotheses have been advanced to account for the inheritance of the disease. Bowman<sup>13</sup> suggested that an inherited disposition of the vessels or nerves might be supposed to be the primary seat of the disease. Priestley Smith<sup>59</sup> published a small pedigree in which father and daughter had abnormally small eyeballs. Elliot<sup>60</sup> expressed the same idea. Nettleship<sup>37</sup> suggested that there might be an inherited disproportion of the cornea, ciliary body and lens, or the inheritance of weakness in the lamina cribrosa. The combination of hereditary glaucoma and myopia has been discussed.

Mousselevitch<sup>61</sup> implicated the endocrine glands. He described a woman in whom glaucoma developed in the right eye two weeks after the first confinement and in the left eye after the second confinement. Her mother also became blind after childbirth. Her brother and grandfather were afflicted with glaucoma. Franceschetti<sup>47</sup> expressed the belief that only the tendency to glaucoma is inherited.

#### PRESENTATION OF PEDIGREES

Fifty-one patients, belonging to 30 different families, have come under our observation. Some were patients of the late Dr. Mark J. Schoenberg. Forty-eight additional persons with known glaucoma have been found in this group but have not been examined by us.

The patients have been classified into four groups according to type, namely, acute congestive glaucoma, chronic congestive glaucoma, chronic simple glaucoma with congestive attacks and chronic simple glaucoma. This classification follows that of Schmidt-Rimpler,<sup>62</sup> who recognized the existence of a congestive phase in certain cases of chronic simple glaucoma. The reasons for the use of this nomenclature are given elsewhere.<sup>61</sup> Pupillographic examinations were carried out by Dr. Otto Lowenstein on 6 glaucomatous patients and 14 normal relatives. For all the patients and for 3 of the relatives the findings were similar to those found in cases of primary glaucoma.<sup>63</sup> In addition to the customary

58 Le Quang, R. Hereditary Glaucoma, Paris, Ed. Jol, 1935.

59 Smith, P. An Instance of Hereditary Glaucoma and Its Cause, *Ophth Rev* 13 215-226, 1894.

60 Elliot, R. H. A Treatise on Glaucoma, London, Oxford University Press, 1922, pp 134-136.

61 Mousselevitch, cited by Preobrazhenskiy<sup>22</sup>

62 Schmidt-Rimpler, H. Glaukom und Ophthalmomalacia, in Graefe, A., and Saemisch, T. Handbuch der gesamten Augenheilkunde, Leipzig, W. Engelmann, 1908, vol 6, pt 1.

63 Lowenstein, O., and Schoenberg, M. J. Nervous Factor in the Origin of Simple Glaucoma, *Arch Ophth* 31 384-391 (May) 1944.

provocative tests, some of the patients were subjected to the Knapp epinephrine test <sup>64</sup> and to the jugular compression test of Schoenberg <sup>65</sup>

**FAMILY 1**—Both the father and the mother had glaucoma. The mother refused surgical treatment and became blind at the age of 65. Of their 6 children, 3 have glaucoma. All but Sam have chronic simple glaucoma. Sam has chronic simple glaucoma with congestive attacks, which began after the institution of miotic therapy. Louis was followed for fourteen years. The grandchildren are not old enough to permit one to form any conclusions on the basis of this pedigree.

**FAMILY 2**—Bertha has chronic simple glaucoma which began with an acute congestive attack in both eyes following use of atropine for refraction. Her case demonstrates that even juvenile glaucoma may take a benign course. Her aunt (Anna) has chronic simple glaucoma. Bertha's visual fields continued to contract, although the tension had been reduced to 11 and 18 mm. Her sister, who also has dementia precox, had an acute congestive attack shortly after confinement in a psychiatric institution. According to the history, Bertha's mother had glaucoma. Constitutional diseases, such as hypertensive vascular disease, toxic goiter and disease of the coronary arteries are prevalent in this family. Bertha was observed for thirteen years and her aunt for twenty-one years.

**FAMILY 3**—Esther and her father, Jacob, both have chronic simple glaucoma. The former has emmetropia and the latter high hypermetropia. In both, the disease pursues a moderately severe course. Jacob was kept under observation for twenty-one years. The onset of glaucoma in Esther's left eye was at the age of 34, while the disease developed in the right eye at the age of 36. This case illustrates the futility of attempting to draw a sharp line of distinction between adult and juvenile glaucoma by using the age of 35 as the dividing line. Families 2 and 3 show anticipation.

**FAMILY 4**—Two sisters have chronic simple glaucoma of a mild form. Several other members of the family have the disease. Both sisters are asymptomatic, and their disease was discovered because of the history of glaucoma in the family. Neither showed increase of tension after use of homatropine. Carrie's left eye, however, showed a positive reaction to the jugular compression test. The glaucoma in her right eye began sixteen years after the onset in the left eye. Carrie was followed for twenty-five years and Rosa for fifteen years. These cases show how mild a course chronic simple glaucoma may pursue in certain cases.

**FAMILY 5**—Two sisters have mild glaucoma. In 1 of them, Babette, the disease is of the chronic simple type, while in the other, Gisella, acute glaucoma developed after use of atropine but responded well to miotics. The third sister, Ethel, had two acute attacks in the same eye. Ethel was observed for thirteen years and Gisella for fourteen years. At the age of 60 their father had onset of chronic simple glaucoma, which necessitated surgical intervention, but he retained his vision up to the time of his death, at the age of 80. One sister and 2 children of another sister have convergent strabismus. The entire family displays a strong tendency to psychoneurosis.

**FAMILY 6**—All 3 sisters have acute congestive glaucoma. The ages of onset were 17, 39 and 71 years, respectively. Their mother first had glaucoma at the age of 60. Thus, 2 sisters show anticipation, while the third one does not. Of

<sup>64</sup> Knapp, A. The Action of Adrenalin on the Glaucomatous Eye, *Arch Ophth* 50 550-559 (Nov) 1927.

<sup>65</sup> Schoenberg, M. J. Experimental Study of Intraocular Pressure and Ocular Drainage, *J. A. M. A.* 61 1098-1103 (Sept 27) 1913.

5 eyes with glaucoma in this sibship, 3, belonging to 3 different members, had to be enucleated because of poor response to iridectomy. One eye showed a good result after cyclodialysis. One of the sisters (Rose) maintained a tension of between 35 and 40 mm of mercury for over twenty years without loss of field.

**FAMILY 7**—The disease in father (Abraham) and daughter (Shoshana) began as asymptomatic chronic simple glaucoma. The father had monocular glaucoma. Four months after treatment with pilocarpine was instituted, he began to have congestive attacks. He was observed for thirteen years. The daughter had an acute attack in the right eye one day after cyclodialysis of the left eye. She was followed for ten years. All 3 affected eyes reacted poorly to operation on the iris. The daughter's right eye behaved relatively well for seven years after cyclodialysis. Cases of this type, which begin as chronic simple glaucoma, respond poorly to miotics, lose the fields rapidly and go on to blindness after surgical measures involving trauma to the iris, are, fortunately, infrequent. In the hereditary group there was 1 other such case (family 27), and 8 additional cases occurred among the remaining 323 cases of glaucoma in our series.

**FAMILY 8**—Lottie has mild glaucoma, while her brother, John, has a severe form of the disease. A presumptive diagnosis of glaucoma was made for Lottie's condition twenty-five years ago. She suffers from recurrent blurring and ocular discomfort. On several occasions the tension was found to be elevated. Pupillographic examination showed a curve similar to that found for primary glaucoma. She has been under observation for eighteen years, has retained normal vision in each eye and has not lost any of the visual field. The brother, on the other hand, has become blind in one eye and has retained only a central island of vision of 5 degrees in the other. He has been observed for seventeen years. Their father had onset of glaucoma at the age of 67, but none of his nine brothers and sisters had the disease. A case such as Lottie's shows the importance of differentiating between the two terms which are frequently used synonymously—"early glaucoma" and "mild glaucoma." Only after prolonged observation can one be certain that a case belongs to the mild group.

**FAMILY 9**—Armen has chronic simple glaucoma, which was discovered after serious contraction of the fields had already developed. Ilona his niece, had an acute attack in her right eye while in the hospital, awaiting sympathectomy for hypertensive vascular disease. The other eye reacted positively to the lability test and is being treated prophylactically at another clinic.

**FAMILY 10**—Lottie has chronic simple glaucoma of the right eye and chronic congestive glaucoma of the left eye. The disease is mild, but the fields showed early involvement of the central area. Her sister has the syndrome of recurrent glaucomatocyclitic crises in the left eye. This disease is characterized by recurring attacks of unilateral glaucoma, associated with mild cyclitic signs, and has been described elsewhere<sup>66</sup>.

**FAMILY 11**—Ralph is the only one of 4 siblings to have glaucoma. His mother, 4 of her brothers and 1 of her sisters had the disease. Ralph's disease began as asymptomatic glaucoma simplex, but subacute congestive attacks developed after the institution of pilocarpine therapy.

**FAMILY 12**—Kurt has asymptomatic chronic simple glaucoma. He has myopia of about 6 D in each eye. His mother and a second cousin also had the disease. After bilateral cyclodialysis in 1936, the tension of the right eye became subnormal, while the left eye continued to have a high normal tension, yet the loss

<sup>66</sup> Posner, A, and Schlossman, A. Recurrent Unilateral Glaucoma with Mild Cyclitic Symptoms, *Arch Ophth* 39 517 (April) 1948.

of field has been the same in the two eyes. The occasional use of 10 per cent phenylephrine hydrochloride (neo-synephrine hydrochloride®) in the left eye enhances the effectiveness of pilocarpine.

FAMILY 13—Reva has chronic simple glaucoma of the right eye and chronic congestive glaucoma of the left eye. Anna has chronic congestive glaucoma of the right eye and acute congestive glaucoma of the left eye. Reva's left eye has glaucoma-free intervals, but the pupillographic curve during such an interval showed a curve for both eyes similar to that found for primary glaucoma. Anna's right eye also has glaucoma-free intervals. Both sisters have diabetes, arteriosclerosis and cataracts. Reva has been followed for nine years and Anna for twenty years.

FAMILY 14—Ruth has asymptomatic chronic simple glaucoma of both eyes. The disease was discovered during routine examination, which was made because of the family history. Her mother, 3 of her sisters and 1 brother have the disease.

FAMILY 15—Edith had onset of bilateral chronic simple glaucoma at the age of 78. In 1 of her brothers and in 1 sister glaucoma developed at the ages of 55 and 45, respectively. All the affected siblings were childless.

FAMILY 16—Lena had acute congestive glaucoma of the right eye. The left eye remained normal until her death, seventeen years later. Her 2 sisters had glaucoma. However, their children, all of whom are over 40, are free from the disease.

FAMILY 17—Nicholas has mild chronic congestive glaucoma of the right eye. His mother had an attack of acute glaucoma at the age of 80, after the instillation of atropine for treatment of cataract. There are no other cases of glaucoma in the family.

FAMILY 18—Abraham has bilateral chronic simple glaucoma. One sister and his paternal grandfather's brother had the disease.

FAMILY 19—Herbert had onset of bilateral chronic congestive glaucoma at the age of 25. In his mother the disease appeared at the age of 50. This pedigree shows anticipation.

FAMILY 20—Two sisters, Fannie and Minnie, have bilateral chronic simple glaucoma. The third sister is normal. Their father had onset of glaucoma at the age of 75. This pedigree shows anticipation with respect to adult glaucoma.

FAMILY 21—Two sisters, Gussie and Norma, have mild glaucoma. Norma has chronic simple glaucoma of the left eye, but pupillographic studies show a similar curve for the two eyes. Gussie has chronic simple glaucoma of the right eye and chronic congestive glaucoma of the left eye. The onset in the right eye was eleven years later than that in the left eye. Norma has been followed for four years and Gussie for nine years.

FAMILY 22—Marcus has asymptomatic bilateral chronic simple glaucoma. His mother had the same disease.

FAMILY 23—In Renate acute glaucoma of the left eye developed at the age of 68 after facial erysipelas. Two of the patient's sisters, as well as their grandmother, have the disease.

FAMILY 24—Sonja has bilateral congestive glaucoma of a mild form. Her mother had glaucoma. The patient and several other members of her family have hypertensive vascular disease.

FAMILY 25—Solomon has bilateral chronic simple glaucoma. His brother also had the disease. His son, who is 51 years of age, does not have glaucoma.

FAMILY 26—Bella had bilateral chronic congestive glaucoma, while her niece Bessie had acute congestive glaucoma in the left eye and chronic congestive glaucoma in the right eye

FAMILY 27—Mollie has bilateral chronic simple glaucoma. The right eye became blind after iridencleisis. In this respect, her case is similar to the 2 cases described in family 7. Her brother also has glaucoma.

FAMILY 28—Two first cousins had monocular chronic congestive glaucoma. In each case the right eye was affected and the glaucoma ran a mild course. Both the patients had hypermetropia of a high degree. Regina was followed for twelve years and Celia for five years. The striking similarity between these 2 cases is added evidence of a genetic basis of the disease in the two cousins.

FAMILY 29—Two first cousins had bilateral chronic simple glaucoma.

FAMILY 30—Two first cousins have congestive glaucoma. Abraham had an acute attack in his left eye, but deep cupping was already present—evidence of a preexisting asymptomatic glaucoma simplex in that eye. Rose has chronic congestive glaucoma in the left eye. The right eye remained normal until instillation of 0.5 per cent homatropine hydrobromide precipitated an acute congestive attack six years after the onset of glaucoma in the other eye.

#### MECHANISMS OF HEREDITY

The pedigrees reported in this paper, as well as those found in the literature, should leave no doubt in one's mind as to the familial nature of a certain proportion of cases of glaucoma. Surely, the incidence of glaucoma in these families is far greater than that in the general population. The presence of the same disease in two or more generations of the same family is evidence that heredity plays an important role in the pathogenesis of glaucoma. Even the occurrence of the disease in two or more members of the same generation is presumptive evidence of a hereditary tendency. The chances of glaucoma occurring sporadically in more than one member of a family similar in size to those reported in this paper are negligible.

The fact that a condition becomes manifest late in life, as is the case with glaucoma, is not a valid argument against its being considered hereditary. Through his studies on identical twins, Vogt<sup>67</sup> produced conclusive evidence of the hereditary nature of cataract and other senile conditions. What is more, he showed that twins exhibit a striking similarity in the appearance of these conditions as seen with the slit lamp.

According to the modern concepts of heredity, the gene is the unit of inheritance. The genes occupy more or less fixed positions in the chromosomes. The latter occur in homologous pairs in the cells of the body. One member of each pair is derived from the father and the other from the mother. Only 2 of 48 chromosomes form a nonhomologous pair. These are the X and Y chromosomes, which carry the sex-

<sup>67</sup> Vogt, A. Lehrbuch und Atlas der Spaltlampen-Mikroskopie des Lebenden Auges, Zurich, 1942, vol. 3, pp. 933-949.

linked genes. The X chromosome carries a full complement of genes, while the Y chromosome carries relatively few.

There are three main types of heredity—dominant, recessive and sex-linked. In dominant heredity, it is necessary for only one pair of genes to carry the defect in order for the latter to become manifest. If a person who has a dominant defect marries a normal person, 50 per cent of the progeny, statistically speaking, will inherit the defect (fig. 1). Such affected parents and their affected offspring are heterozygous because the two homologous genes are not alike, one carries the trait and the other is free from it. If two such heterozygous persons mate, 75 per cent of their children will show the trait. One-half the offspring will be heterozygous for the defect, one-fourth will be homozygous, and the remaining one-fourth will be normal. The homozygous offspring

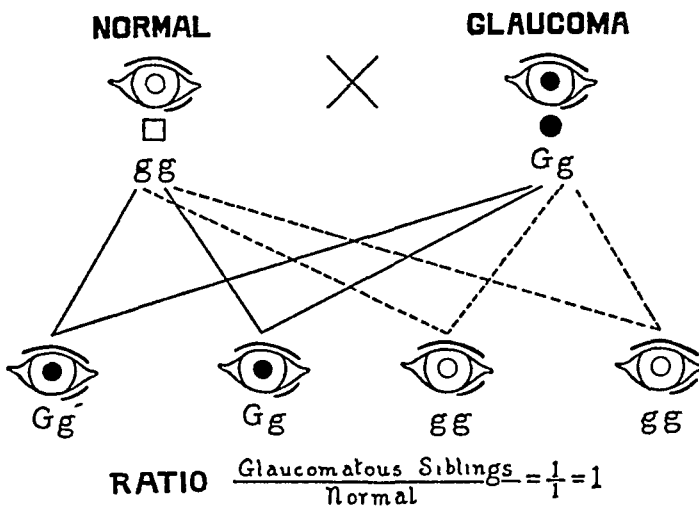


Fig. 1—Theoretic ratio of complete dominance

are those who carry two defective genes—one derived from the father and one from the mother.

In recessive heredity, the trait or disease does not become manifest unless both genes carry the defect. In other words, it occurs only in persons who are homozygous. Thus, many persons in the general population may carry the recessive gene for generations, yet the disease may become manifest only if one of these persons marries another person who carries the same gene.

Our family trees and all but 2 pedigrees in the literature appear to show a dominant heredity. For this reason, it is fitting to discuss more fully the mechanisms involved in this form of inheritance. Theoretically, if complete dominance were present, at least 1 case of glaucoma should occur in each generation. It has been shown, however, not only in human genetics but also in well controlled animal experiments, that a defect may fail to appear in one generation but may continue to manifest itself as a dominant in subsequent generations. This phenom-



enon of skipping a generation is known as "lack of penetrance" This means that the disease fails to express itself in the soma, even though the gene is present in the germ cell, this presence is evident from the transmission of the disease to the succeeding generation It is possible for glaucoma to occur in such a mild form that it can be detected only by use of pupillography, by provocative tests, or by prolonged periods of observation The differences in the severity of the disease may be accounted for in some cases by differences in the "expressivity" of the gene The appearance of glaucoma late in life may be regarded as demonstrating a relative lack of expressivity Since glaucoma may

*Data for Determination of Penetrance*

Family No	Total No Siblings	Siblings with Glaucoma	Sibships with No Glaucomatous Parent	Sibships with One Glaucoma tous Parent	Sibships with One Glaucoma tous Parent and No Glaucomatous Children
2	9	4		1	
3	20	7	1	3	
4	13	4		3	
5	3	3		1	
6	4	3		1	
7	8	3		2	
8	5	2		1	1
9	8	3	1	1	
10	5	2		1	1
11	6	1		1	1
12	8	2	1	1	
14	8	4		1	
15	10	3	1		
20	8	2		1	2
24	5	2	1	1	
28	5	1		1	
Total	125	46	5	20	5

begin as late as from 70 to 80 years of age, it is impossible to be certain whether a person who dies at an earlier age would have manifested the disease Since the concepts of expressivity and penetrance, at least as applied to glaucoma, may imply merely quantitative differences, they cannot be sharply differentiated from each other

The genetic approach to the study of disease in human beings is complicated by the small size of the average pedigree and by variability in penetrance According to Gates,<sup>68</sup> "in short pedigrees the real method or methods of inheritance may emerge only after comparing several pedigrees of the same condition" Following the suggestion

<sup>68</sup> Gates, R R Human Genetics, New York, The Macmillan Company, 1946, vol 1, p 4

of Dr M Demerec and Dr H B Newcombe, of the Carnegie Institution of Washington, department of genetics, we have pooled our material for statistical purposes, in order to gain better insight into the mechanisms of heredity

The table shows the method used for determining the degree of penetrance of the gene for glaucoma. Only 16 pedigrees contained sufficient data to be used for this purpose. Even in these family trees, we discarded those sibships in which information on the condition of the parents' eyes was indefinite or in which the parent died before the age of 40. We also discarded those sibships in which the children did not reach the age of 40, except when one of the members manifested glaucoma at an earlier age.

Alternative methods of arriving at penetrance values are compared. In dominant heredity, one must assume that nearly all the affected persons are heterozygous. For this reason, the expected ratio of glaucomatous to normal sibling should be 1:1 (fig. 1). If the number of affected persons is significantly less than 50 per cent, the difference may be regarded as lack of penetrance. Of a total of 125 siblings, there were 46 siblings with glaucoma. If penetrance were 100 per cent, the expected number of glaucomatous persons would be 62. The ratio of 46:62, or 74 per cent, denotes the average penetrance at the age of 40 (fig. 2).

The other method of studying penetrance is a comparison of the number of sibships with one glaucomatous parent and the number neither of whose parents has glaucoma. If penetrance were 100 per cent, no generation should entirely escape the disease. If neither parent has glaucoma and the disease appears in 2 of the children, one assumes that the germ plasma of one of the parents contains the gene for glaucoma. The totals in the table show 20 sibships in which one parent had glaucoma, as compared with 5 sibships in which neither parent had glaucoma. Thus, 20 of 25 sibships showed complete penetrance. This makes the average penetrance for the group 80 per cent (fig. 2).

Both these methods probably overestimate penetrance. While our pedigrees include only the families with 2 or more affected members, there undoubtedly are families with one affected member in which other members are genetically glaucomatous without exhibiting the disease clinically. Even though the two methods used yielded similar values for the degree of penetrance in cases of hereditary glaucoma, it should be remembered that these figures (74 and 80 per cent) are, at best, rough estimations because of the small number of cases available for this study.<sup>69</sup>

<sup>69</sup> For this reason, no correction was made for random sampling, such as the exclusion of the prepositus patient (the one who brought the family to the attention of the physician).

The lack of penetrance of the gene has definite clinical implications in the study of the behavior of glaucoma. It shows, by the genetic method, that a person may fail to show any clinical manifestations of the disease and still be genetically glaucomatous.

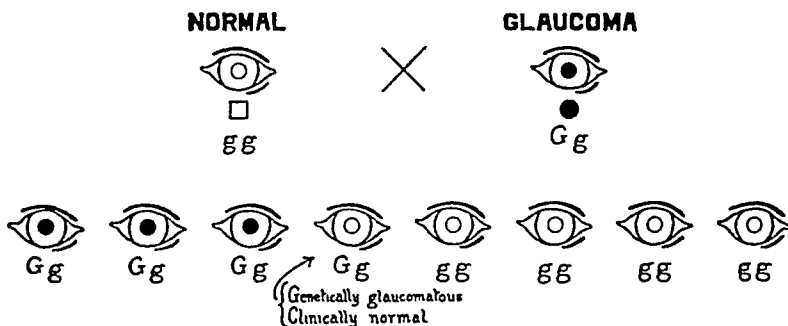
One of the pedigrees (family 8) shows probably a dominant mutation. The father of Lottie and John was the only sib with glaucoma.

**PENETRANCE } 74-80%**  
**EXPRESSIVITY }**

### DETERMINATION

(1) **PENETRANCE**  $\frac{\text{Glaucomatous Siblings}}{\text{Expected Glaucomatous Siblings}} = \frac{46}{62} = 74\%$

\* If ratio were 1:1 (Complete Dominance) 62 of 125 would have Glaucoma.



(2) **PENETRANCE**  $\frac{\text{Sibships with glaucoma in 1 parent}}{\text{Total Sibships}} = \frac{20}{25} = 80\%$

\* Sibships with glaucoma in 1 parent = 20  
Sibships with no glaucoma in either parent = 5  
Total = 25

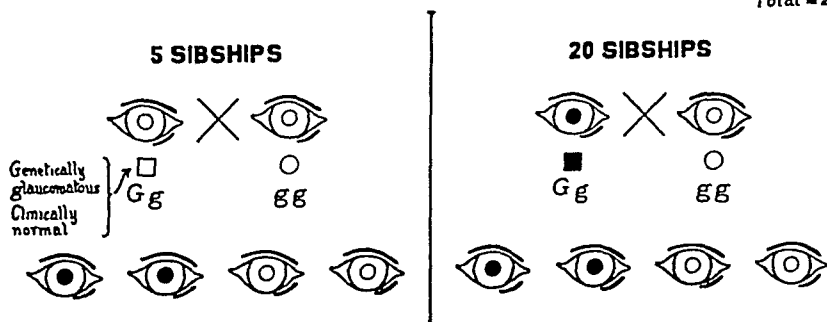


Fig 2—Actual ratio of incomplete dominance

among 10 brothers and sisters. His father and mother lived to be over 90 years of age and were normal. The chances of dominant heredity when only 1 of 10 siblings is affected is less than 1 per cent. We may assume, therefore, that a gene was changed in such a way that it now transmits glaucoma in a dominant manner.

In family 1, there was a marriage between two persons in whom glaucoma developed in late life. Up to the present, 3 of their 6 children have exhibited the disease. If both parents are heterozygous for glaucoma, the expected ratio is 3 glaucomatous children to 1 normal child. Some of the affected members of the third generation are probably homozygous for the disease. Since all children of homozygous parents should inherit glaucoma, it will be interesting to watch their progeny (generation 4).

Families 28, 29 and 30 show glaucoma in 2 first cousins. Family 30 is the only one for which we have an adequate pedigree. The others were included because the clinical course of the affected patients was followed for a long time. It is impossible to draw conclusions from such incomplete material. The occurrence of glaucoma in family 30 may represent dominant heredity with a very low penetrance, or the inheritance may be recessive. This strongly suggests the possibility of more than one type of inheritance in glaucoma, since the chance of coincidence is negligible. In discussing the role of dominant and recessive heredity in evolution, Morgan<sup>70</sup> stated that there is no sharp contrast between dominant and recessive genes.

Many genes classified as recessive produce some effect in hybrid combination on the character most affected. It follows that there may be no essential difference between the kinds of genes in question.

This raises the question of the possibility of recessive inheritance for glaucoma in general. The literature does not enlighten one on this point. From small pedigrees it is impossible to draw any conclusions about recessive inheritance, unless consanguinity is present. In order properly to study this type of heredity, one must investigate large numbers of members of a family and compare the incidence of glaucoma in this family with that in the general population.<sup>71</sup> Sufficient data are not available to justify any conclusions as to the role of recessive heredity in glaucoma in general. In recessive heredity, the gene may become widespread in the population without manifesting the disease except as a result of chance mating of carriers (heterozygous persons). This may be one way of accounting for sporadic cases. For the sake of speculation, let us assume, for the moment, that all glaucoma is hereditary. If the incidence of the disease is 0.25 per cent of the general population, then 9.5 per cent of the entire population would carry one gene for glaucoma (heterozygous). Thus the possibility of chance matings is not inconsiderable.

<sup>70</sup> Morgan, T. H. *Evolution and Genetics*, Princeton, N. J., Princeton University Press, 1925, p. 15.

<sup>71</sup> Reudin, E. *Zur Vererbung und Neuentstehung der Dementia praecox*, Berlin, Julius Springer, 1916, in *Monographien aus dem Gesamtgebiet der Neurologie und Psychiatrie*, 1916, no. 12.

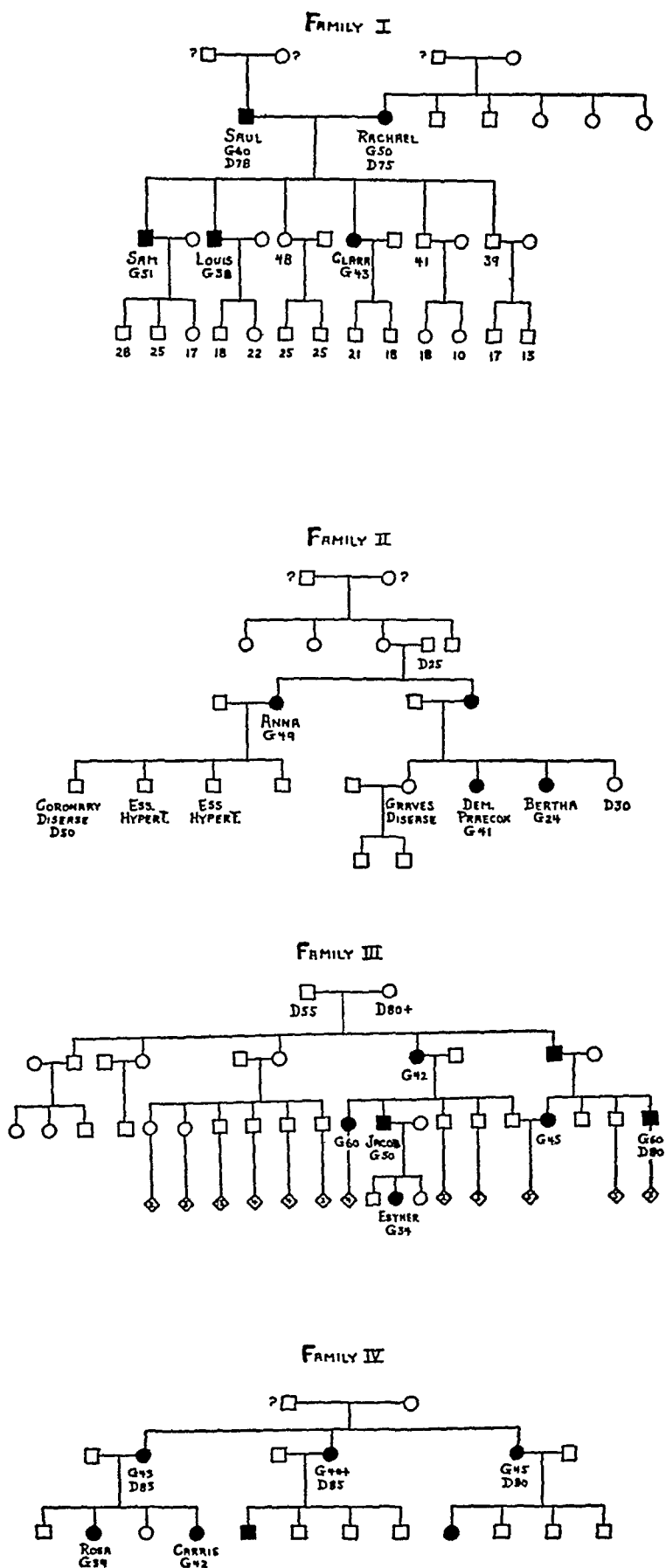


Fig 3—Pedigrees for families 1 to 4

## COMMENT

The group of hereditary glaucoma forms a representative cross section of cases of the disease in general. In several instances the disease began as chronic simple glaucoma but was complicated by congestive attacks after prolonged use of miotics. Many gradations in severity were encountered—from those cases in which the disease remained mild over many years to those in which it resulted in blindness in a relatively short time.

Of 373 patients with glaucoma, 51 had demonstrable hereditary tendencies—an incidence of 13.7 per cent of all the patients with glaucoma available for our study. Of 91 eyes, 52 had chronic simple glaucoma, 10 had chronic congestive glaucoma and 14 had acute glaucoma.

A review of the case histories reveals that in many families there were similarities in the behavior of the disease with respect to type, refractive error, severity and response to surgical treatment. In 4 families the glaucoma was of the chronic simple type in all members examined. In 2 families all members had chronic simple glaucoma, but congestive attacks occurred in some of them. In 3 families all members had congestive glaucoma. One of these (family 6) is interesting because all 3 sisters had acute congestive glaucoma, although the first attack occurred at 17, 39 and 71, years of age respectively. In several families, however, the type of glaucoma differed in the different members.

The refractive error was similar in 9 families and significantly different in 4 families. This group affords a rare opportunity for the study of mild glaucoma, since some of the cases would not have been discovered were it not for the presence of glaucoma in other members of the family. In families 4, 5 and 8, the glaucoma was exceptionally mild in all but 1 member. It ran a moderately severe course in all the members of families 3 and 19. In family 7, the glaucoma displayed an unusually severe course in the affected eyes of both members. Moreover, both father and daughter reacted poorly to operation on the iris. In family 6, 3 of the 5 affected eyes (belonging to 3 different members) had to be enucleated because of poor response to surgical procedures on the iris.

These examples are at least suggestive that not only the disease but also the pattern of its behavior may be influenced by heredity in some cases. Since the knowledge of a case history of one member may serve as an aid in the treatment of another affected member, it is advisable for the ophthalmologist to acquaint himself, whenever possible, with the histories of all members of the family who have the disease. This is especially important when one member has shown dis-

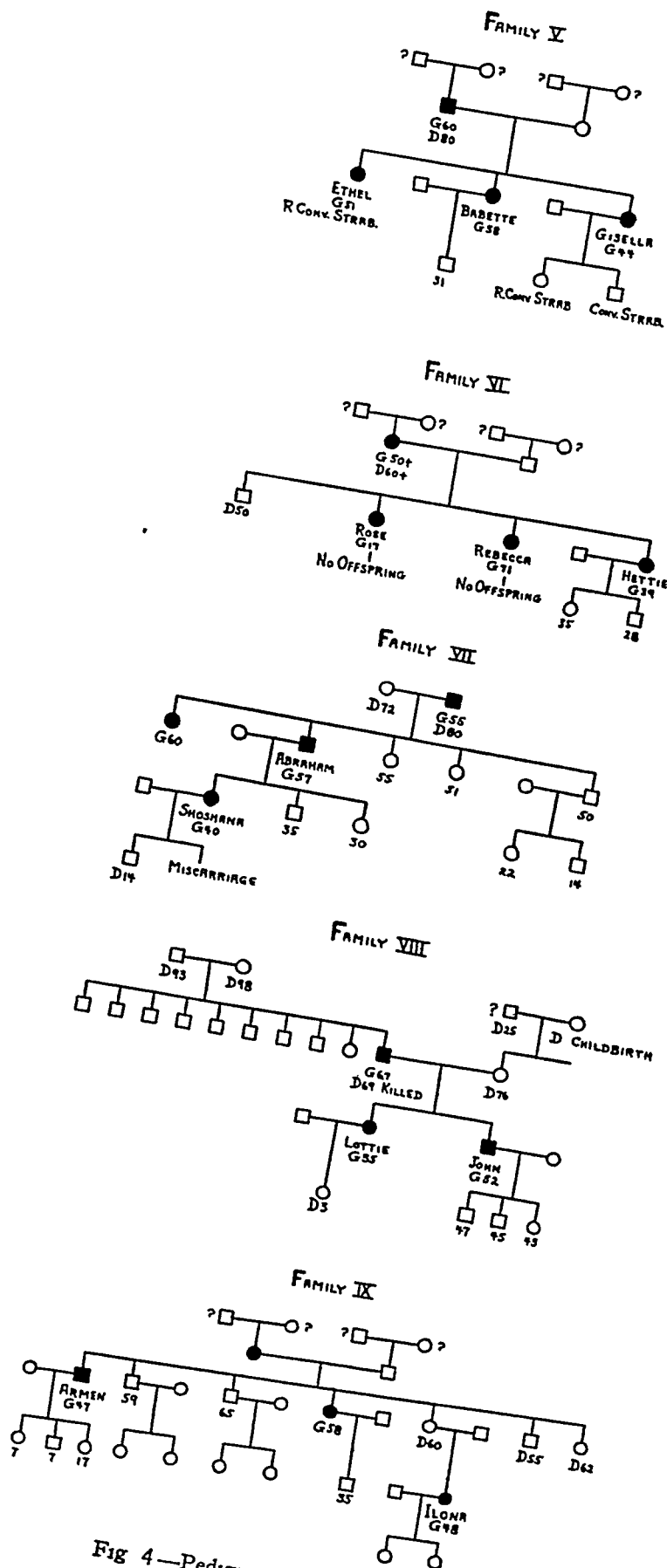


Fig 4—Pedigrees for families 5 to 9

astrous results following surgical procedures on the iris. In such a case it may be advisable to use cyclodialysis as the operation of choice. If the disease has proved mild in other members of the same family and the course of the patient's glaucoma appears to be similar, the physician may reassure his patient that his disease will probably follow a similar pattern.

The hereditary approach may help to bring primary glaucoma into relation with other types of glaucoma. Ever since von Graefe called attention to "amaurosis with excavation," the role of glaucoma without hypertension has been a subject of controversy. Elschnig<sup>72</sup> reported a family in which 2 first cousins had glaucoma without hypertension, while an uncle suffered from glaucoma with hypertension. Recently, Sjogren<sup>73</sup> has attempted to show, on a clinical basis, that simple glaucoma displays wide variations in symptomatology, and that glaucoma without hypertension may be regarded as one type of primary glaucoma. Glaucoma which develops after cataract extraction should not, as a matter of course, be classified as secondary. We have reported several cases elsewhere<sup>51</sup> in which a positive result in the provocative tests in the opposite eye or the occurrence of primary glaucoma in the eye not operated on proved that the disease was probably primary glaucoma. The father of one of our patients with primary glaucoma (N. W.) had ocular hypertension following an uncomplicated cataract extraction. A knowledge of the family history should be helpful in evaluating such a case. Certain cases of recurrent unilateral glaucoma with mild cyclitic signs, a condition which we have called the syndrome of recurrent glaucomatocyclitic crises,<sup>66</sup> probably form an intermediate group between primary and secondary glaucoma. Its relation to primary glaucoma is further evidenced by the pedigree of family X. Of 2 affected sisters, 1 has primary glaucoma and the other the syndrome of glaucomatocyclitic crises. Another patient (A. S.) with the latter disease has an aunt with primary glaucoma. The relation of retinitis pigmentosa to primary glaucoma is obscure. There are several pedigrees in the literature in which the association appears. Blessig<sup>74</sup> reported a sibship of 9 members of whom 2 sisters had chronic simple glaucoma alone, while 2 brothers and 1 sister had pigmentary degeneration without ocular hypertension. We have a patient with retinitis pigmentosa and glaucoma of the congestive type.

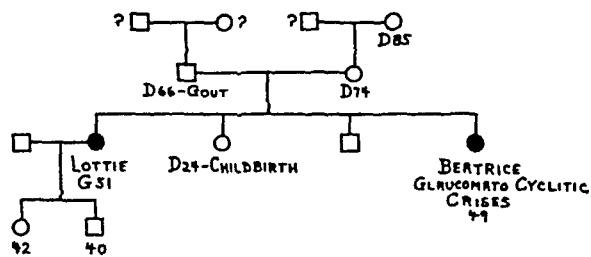
<sup>72</sup> Elschnig, A. Glaucoma Without Hypertension and Hypertension Without Glaucoma, *Ztschr f Augenh* **52** 287-296, 1924.

<sup>73</sup> Sjogren, H. A Study in Pseudoglaucoma, *Acta ophthal* **24** 239-294, 1946.

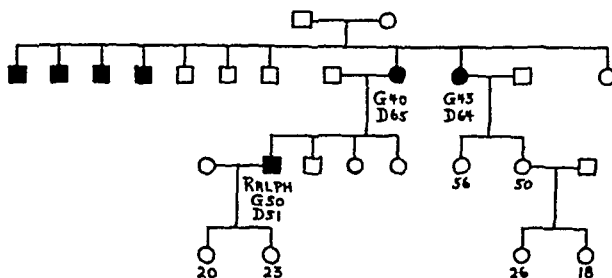
<sup>74</sup> Blessig, E. Alternating Occurrence of Glaucoma Simplex and Retinitis Pigmentosa in a Series of Siblings, *St. Peterberg med Wchnschr* **21** 105-106, 1901.



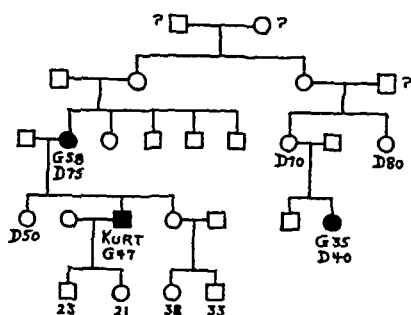
# FAMILY X



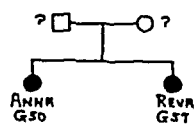
# FAMILY XI



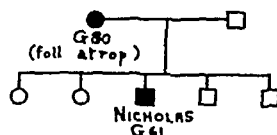
# FAMILY XII



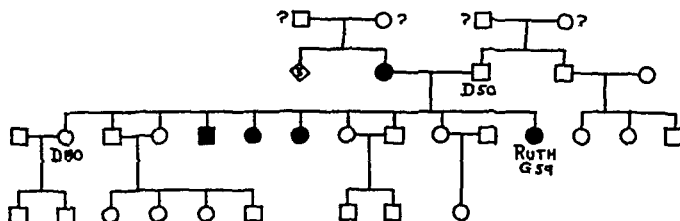
# FAMILY XIII



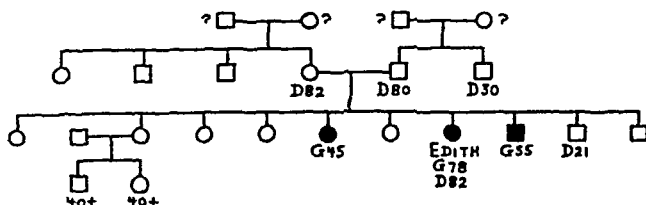
# FAMILY XVII



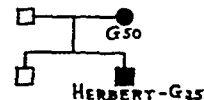
# FAMILY XIV



# FAMILY XV



# FAMILY XIX



# FAMILY XXII

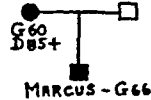


Fig 5—Pedigrees for families 10 to 15, 19 and 22

Two of her sisters have retinitis pigmentosa, but only 1 of them has glaucoma. From a genetic point of view, these examples show that primary glaucoma cannot be sharply differentiated from secondary glaucoma on a clinical basis alone. This evidence is in agreement with the everyday experience of the ophthalmologist.

The occurrence of hydrophthalmos and primary glaucoma in the same family has been reported in 4 pedigrees from the literature. We have previously stated our reasons for believing that the two diseases are not related. It is possible, however, that two clinically different diseases may be associated genetically by linkage of the genes. This may also be the case with retinitis pigmentosa and strabismus.

Among constitutional diseases, hypertensive vascular disease and diabetes are those most commonly associated with glaucoma. Elwyn<sup>75</sup> pointed out that in all three diseases there is a disturbance of the regulatory function. In family 2, 4 members have glaucoma, 2 have hypertensive vascular disease, 1 has coronary disease, 1 dementia precox, and 1, toxic goiter. Another pedigree, family 13, shows 2 sisters with glaucoma and diabetes. Many pedigrees of patients from the nonhereditary group exhibit a strikingly large incidence of metabolic disorders among the nonaffected members. It is possible that the gene for glaucoma is somehow related to the gene or genes for other regulatory diseases.

It is difficult to determine the exact manner in which heredity affects the eye. Many anatomic variations and abnormalities have been implicated. Some of them were mentioned in a previous section. The belief is prevalent that hypermetropia is a predisposing factor in glaucoma. While it is true that hypermetropia may be inherited, we have shown that the refractive errors found among patients with glaucoma follow the same distribution as those in the general population.<sup>51</sup> Holst<sup>76</sup> supported this point of view.

It was previously shown that some persons are genetically glaucomatous but show no clinical manifestations of the disease. They may have glaucoma at some future time of life, either spontaneously or as the result of a provocative factor, such as instillation of atropine, cataract extraction or emotional disturbances. From this point of view, their normal state may be regarded as a preclinical stage. It would be interesting to find tests which would detect patients who are potentially glaucomatous while they are still clinically normal. Pupillography promises to be of great value in this respect for it enables one to evaluate

75 Elwyn, H. The Pathogenesis of Chronic Simple Glaucoma, *Arch Ophth* 19 966-1008 (June) 1938.

76 Holst, J. C. A Statistical Study of Glaucoma, *Am J Ophth* 30 1267-1276, 1947.

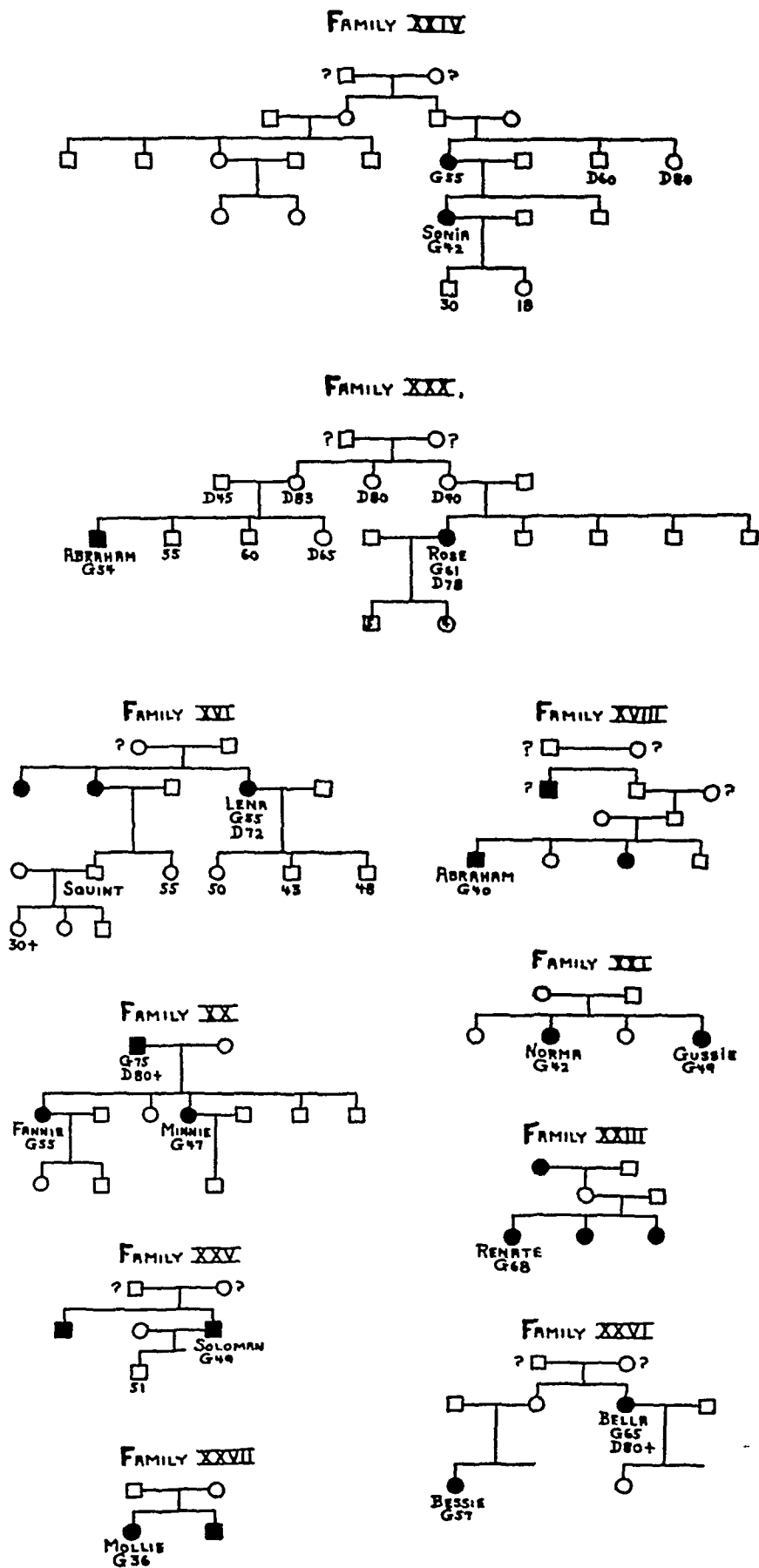


Fig 6—Pedigrees for families 24, 30, 16, 18, 20, 21, 23, 25, 26 and 27

the state of the autonomic nervous system, especially the hypothalamic center. In all the cases of primary glaucoma thus far studied, a pupillographic curve had certain definite characteristics<sup>64</sup> Fourteen normal relatives of glaucomatous patients were subjected to pupillographic studies Three of these persons showed curves similar to those found in cases of primary glaucoma, while all other tests gave negative results Further work along this line is now in progress It is possible that the inherited factor is a disturbance in the central autonomic nervous system

The mechanism of heredity as related to our pedigrees has already been discussed The role of genetics among the sporadic cases cannot be entirely ignored Considering the possibility of low penetrance and low expressivity, it is not unlikely that in some of the sporadic cases the disease is also hereditary It is well known that the same disease may be transmitted in dominant, recessive and sex-linked manner This is true of retinitis pigmentosa and Leber's disease (hereditary optic atrophy) Recessive genes for a given trait may become widespread in the general population without the trait becoming manifest The occurrence of sporadic cases may result from the mating of two persons who carry recessive genes

In view of the extreme degree of hybridization of the human species, it is impossible to make any predictions as to the heredity in a specific case of glaucoma From the eugenic standpoint, one may, however, feel justified in advising a patient with glaucoma in whose family the disease shows dominant heredity against marrying into another family with glaucoma

For a better understanding of the mode of transmission of glaucoma, it is essential to have a large series of good pedigrees The technique of taking pedigrees is simple It is important to obtain the total number and ages of all the siblings in each generation the age of onset of the disease and the age of death of the deceased members We regret that some of our pedigrees are incomplete Since some of the patients were not available for questioning during the past year, a few of these family histories were obtained indirectly through the case records We hope to complete these pedigrees in the near future

Patients are acutely aware of the hereditary potentialities of diseases It behooves the physician to give serious attention both to the psychologic and to the ophthalmologic aspects of the patient's problem Provocative tests and pupillography, when feasible, are of great value, since a negative result helps to reassure the patient and a positive result means an early diagnosis

## SUMMARY

Heredity plays a role in the pathogenesis of glaucoma. Fifty-one, or 13.7 per cent, of 373 unselected cases from private practice showed familial tendencies.

In most families the disease follows a similar course in the various affected members.

All the pedigrees show dominant heredity, except for 1, in which it may be recessive. Some sporadic cases may, on careful analysis, prove to be hereditary.

The genetic approach may be an aid in the early recognition of glaucoma and in the study of the preclinical and mild phases of the disease.

The pedigrees of all but 2 of the families (28 and 29) are included.

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# EXPERIMENTAL STUDIES OF INCLUSION BLENNORRHEA

## Isolation of a Virus

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**I**NCLUSION blennorrhoea is a disease of the conjunctiva related to cervicitis in the female and urethritis in the male, it can be considered a virus venereal disease. The disease occurs most commonly in newborn infants but is also observed in adults. The adult gets the disease by coming in contact with the virus from the urethra or the cervix either by direct contamination or in swimming pools. The clinical manifestations of the disease have been reviewed repeatedly,<sup>1</sup> and it is the purpose of this report to present a study of the probable etiologic agent as a virus rather than to describe further the clinical syndrome.

Thygeson<sup>2</sup> has shown that the virus of inclusion blennorrhoea is morphologically identical with the virus of trachoma except that the matrix of the inclusions of trachoma stain more uniformly with iodine than those of inclusion blennorrhoea. The viruses of these two diseases are similar morphologically to the viruses of lymphogranuloma venereum and psittacosis. Macnie<sup>3</sup> and others have shown that the virus of lymphogranuloma venereum can involve the eye, but thus far no reports can be found that psittacosis has ever invaded this structure.

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Dr. Phillips Thygeson and Dr. Murray Sanders made valuable suggestions and criticisms.

This paper was submitted as a candidate's thesis for membership in the American Ophthalmological Society June 1947.

These studies were conducted under several grants. The major portion of the work was done under a grant from the Knapp Memorial Fund, at the Department of Ophthalmology, Columbia University College of Physicians and Surgeons. Some of the biopsies were conducted under a grant from the John and Mary R. Markle Foundation at the Department of Ophthalmology, State University of Iowa College of Medicine, Iowa City.

1 O'Brien, C. S., and Allen, J. H. Allergic Keratoconjunctivitis, *T. Am. Ophth. Soc.* **40** 170, 1942. Braley, A. E. *Am. J. Ophth.* **21** 1203 (Nov.) 1939. Thygeson, P., and Mengert, W. F. Virus of Inclusion Conjunctivitis. Further Observations, *Arch. Ophth.* **15** 377 (March) 1936. Lindner, K. *Arch. f. Ophth.* **78** 245, 1911. Howard, W. A. *J. Pediat.* **12** 139 (Feb.) 1938.

2 Thygeson, P. *Am. J. Ophth.* **17** 1019 (Nov.) 1934, **14** 455 (July) 1938.

3 Macnie, J. P. Ocular Lymphogranuloma Venereum, *Arch. Ophth.* **25** 255 (Feb.) 1941.

An attempt was made to grow the virus by several biologic methods and to reproduce the disease. I was unable to fill these requirements, but a great deal was learned concerning the virus. Although most of the data presented here are negative, it is felt that the results of this study give some indication of the problem and may be an aid to further investigation.

#### ATTEMPTS TO GROW THE VIRUS

All viruses apparently are obligatory parasites and require living cells for propagation. Most of them have an affinity for certain cells in the body in order to propagate. The virus of lymphogranuloma venereum seems to grow best in the cells of the reticuloendothelial system, but it can be adapted to the mouse brain and also to the yolk sac of the developing hen's egg. The viruses of vaccinia and herpes appear to be predominantly epitheliotrophic, but these also can be adapted to other cells.<sup>4</sup> The viruses of inclusion blennorrhoea and trachoma appear to differ slightly in their cell specificity. The virus of inclusion blennorrhoea seems to be predominantly present in the epithelium of the lower conjunctival sac and involves also a narrow zone in the cervical epithelium.

As has been mentioned before, the virus of inclusion blennorrhoea is similar to the viruses of trachoma, lymphogranuloma venereum and psittacosis. All four of these viruses are similar in several respects, (1) They all stain easily by the Giemsa method, (2) all form distinct inclusion bodies, (3) all occur in two forms, the elementary body form and the initial body form, (4) all seem to have fairly distinct tissue specificity in the human subject, (5) all, with the possible exception of the virus of psittacosis, are sensitive to the sulfonamide drugs, and (6) all fall in a class which seems to be between true viruses, such as those of herpes simplex, vaccinia and poliomyelitis, and the rickettsias. With all these similarities, it would appear that the viruses of both trachoma and inclusion blennorrhoea would follow the same pattern as lymphogranuloma and psittacosis. The virus of lymphogranuloma<sup>5</sup> grows well in the yolk sac of the developing chick embryo, on the chorioallantoic membrane and in tissue culture, however, in many instances in which the virus is obtained from the human patient it must be adapted to its new environment. This may require mutation. With these facts in mind, I then conducted experiments with inclusion blennorrhoea.

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4 Rivers, T. M., and others. *Problem and Trends in Virus Research*, University of Pennsylvania Bicentennial Conference, Philadelphia, University of Pennsylvania Press, 1941.

5 (a) Rake, G., McKee, C. M., and Shaffer, M. F. *Proc. Soc. Exper. Biol. & Med.* **43**: 332 (Feb.) 1940. (b) Sanders, M. J. *Exper. Med.* **71**: 113 (Jan.) 1940.

## METHODS AND PROCEDURES

Epithelial scrapings obtained with a platinum spatula from adults or infants with inclusion blennorrhea were suspended in isotonic sodium chloride solution U S P, neutral nutrient broth, serum ultrafiltrate and sterile distilled water. This material was then (1) inoculated on the chorioallantoic membrane of the developing hen's egg, (2) injected into the yolk of the developing hen's egg, (3) inoculated into fluid tissue cultures and (4) inoculated in normal conjunctival epithelial cells in tissue culture. Biopsy specimens from babies with inclusion blennorrhea were also grown in tissue culture by the Carrel technic.

*Egg Inoculations*—In order to inoculate the chorioallantoic membrane, hen eggs were incubated at 38 C for from five to nine days. A triangular window was then made through the shell over the location of the embryo. A smaller hole was made at the air sac. The air was then withdrawn from the air sac, whereupon the embryo dropped away from the shell membrane at the opening through the shell. The shell membrane was then opened with a sterile knife and the material for inoculation placed inside the shell membrane on the chorioallantoic membrane. The shell was replaced over the area and sealed with paraffin or scotch tape. Both openings in the egg were sealed. The eggs were then replaced in the incubator and opened at periods of from three days to maturity, and the chorioallantoic membrane was removed and studied for lesions. Smears of the embryo and chorioallantoic membrane were also made and stained with Victoria blue and by the Giemsa method.

The yolk sac method of egg inoculation was simpler, it consisted of making a small hole in the egg shell over the air sac and inoculating the material through this opening into the yolk sac by means of a long hypodermic needle. This inoculation was made after an incubation period of from five to nine days. The eggs were opened at periods varying from three days to near maturity, the entire egg being opened so that the embryo was isolated. The embryo was picked up and, with the yolk sac attached, was placed in a sterile Petri dish. Smears or sections, and in many instances both, were made of the embryo. The yolk sac was separated from the embryo and freed of as much yolk as possible, and smears were made of the yolk membrane. These were stained with Victoria blue and by the Giemsa method.

In an attempt to adapt the virus to both the chorioallantoic membrane and the yolk sac of chick embryos, serial passages of both were carried out. This was accomplished by removing either the membrane or the yolk sac, grinding it with a small amount of sterile saline solution and reinoculating eggs with this material. On several occasions during this serial passage, portions of the membranes were used to inoculate baboons, in an effort to determine their infectivity. Fifty-three serial passages were made of inoculated yolk sac and 23 of inoculated chorioallantoic membrane.

*Inoculation of Fluid Tissue Culture*—The tissue culture used in these experiments consisted of balanced saline solution, serum ultrafiltrate and finely divided tissue. The cultures were similar to those used by Sanders<sup>5b</sup> in the propagation of lymphogranuloma virus. Scrapings of the conjunctival epithelium were taken directly from patients with inclusion blennorrhea and inoculated into two fluid cultures. One culture was placed in the incubator at 37 C, and the other was kept at room temperature. A moderate amount of material was removed from the culture, ground in a mortar and inoculated intracerebrally in mice and into the eyes of baboons. Cultures were checked for sterility on ordinary mediums at periodic intervals, and when a tissue culture was contaminated it was either



discarded or filtered and another tissue culture inoculated. These cultures were also passed serially, the incubator cultures were inoculated into mice at three day intervals and the room temperature cultures at five and nine day intervals. All inoculation of cultures attempted by this method failed to infect baboons and did not give rise to encephalitis in mice.

Tissue cultures were inoculated into the mice in most instances by three methods. Approximately 0.02 cc of the tissue culture fluid was injected intracerebrally. The mice were also given from 0.05 to 0.2 cc intraperitoneally, and about half the mice were inoculated with from 0.02 to 0.1 cc intravenously. Each mouse was inoculated by all three methods in an effort to have as much virus as possible present at the site of inoculation in the brain. The intravenously

TABLE 1—*Tissue Culture of Material from Inclusion Blepharitis*

No of Experiments	Source of Material Inclusions	Infective for Baboon	Medium		Gas	Growth and Comment
			Clot *	Fluid †		
2	Cervix		C P	1/10 T S	1/2 Carbon dioxide	Epithelium and leukocytes
4	Conjunctiva of patient with inclusion blepharitis		C P	1/2 T S	1/1 None	Leukocytes
2	Conjunctiva of patient with inclusion blepharitis	Not done	C P	1/2 T S	1/1 Carbon dioxide	Good epithelium, no inclusions
5	Conjunctiva		C P	1/5 T S	1/2 Oxygen and carbon dioxide	Epithelium and fibroblasts, no inclusions
6	Cervix		C P	1/5 T S	1/1 Oxygen and carbon dioxide	No growth except leukocytes baboon inoculations
5	Conjunctiva	Not done	C P	1/5 T S	1/2 Oxygen and carbon dioxide	Epithelium, fibroblasts and leukocytes noninfectious for baboon, transplant epithelium
6	Conjunctiva		C P	1/3 T S	1/1 80% oxygen, 3% carbon dioxide	Epithelium and fibroblasts, noninfectious for baboons
2	Conjunctiva		Fibrin and thrombin, T S	1/1	21% oxygen, 3% carbon dioxide	Epithelium — no inclusions

\* C P indicates chicken plasma, and T S, Tyrode's solution (modified Locke's solution containing magnesium) and serum or serum ultrafiltrate.

injected virus would probably be filtered out in the spleen or in the liver, but it was felt that some of it might reach the point of inoculation in the brain. The intraperitoneal inoculation was given because a large amount of material could be injected into the peritoneal cavity without causing too much shock to the animal.

*Inoculation of Normal Conjunctival Epithelial Cells in Tissue Culture*—Normal conjunctival tissue was obtained from the operating room. This was handled under sterile conditions and after division into small pieces was placed in a Carrel flask and secured by chicken plasma. The nutrient material overlying the tissue in the flask was either normal serum or serum ultrafiltrate plus a balanced saline solution (Tyrode's). Tissue cultures were allowed to grow at incubator temperature until a fair growth of epithelium was obtained. The supernatant fluid was then removed and replaced with a solution consisting of balanced saline solution and serum ultrafiltrate to which scrapings from an eye with inclusion blepharitis

had been added. This was allowed to remain in the incubator for from one to seven days. Some of the preparations were stained by the Giemsa method and studied for the presence of inclusion bodies, while others were removed and the material was inoculated into the eyes of baboons.

*Tissue Culture of Inclusion Conjunctivitis*—Biopsies of the conjunctiva were made on patients with inclusion blennorrhea, and biopsies of cervical tissue, from mothers whose babies had inclusion blennorrhea. This tissue was handled by a method similar to that reported by Thygeson<sup>6</sup> with trachoma. Epithelial growth was obtained in nearly all instances. These cultures were handled in several ways. In some of them the supernatant fluid was removed and inoculated into baboons' eyes. In some the tissue was removed and inoculated into baboons' eyes after growth had been obtained. Some were stained and studied for the presence of inclusions bodies (table 1).

*Variation in Tissue Culture Mediums*—Apparently, a substance present in the normal conjunctiva which made it possible for cells to be infected with the virus was not present in the tissue culture. Therefore, numerous amino acids were added to the tissue culture in order to stimulate epithelial growth and possibly supply the missing substance.

#### RESULTS

The direct inoculation of a chorioallantoic membrane gave entirely negative results, since no demonstrative growth of virus was obtained. On occasion, small foci could be found on the membranes which were suggestive, but when they were examined in smears microscopically no inclusions could be demonstrated by Giemsa's method or with Victoria blue.

The direct inoculation of yolk sac failed to propagate the virus, although by similar technic the virus of lymphogranuloma venereum was successfully grown. Blind passage in eggs all failed to yield the virus. The yolk sac was ground and the material inoculated into baboons' eyes. Numerous smears of yolk sacs were made and stained by the Giemsa method and with Victoria blue but failed to demonstrate the virus. The virus seems to have little or no effect on the developing hen's egg, and when allowed to do so the egg would produce a healthy chick.

The virus was not propagated in fluid tissue culture with any of the types of tissue used. Serial passage in tissue culture failed to infect baboons. No evidence could be demonstrated by the methods used that normal cells of the conjunctival epithelium grown in tissue culture could be infected by the virus of inclusion blennorrhea. Conjunctival epithelium from tissue already infected with the virus of inclusion blennorrhea did not remain infectious in tissue culture with the methods used.

*Comment*—Accepted methods for propagation of the viruses of lymphogranuloma venereum and vaccinia were used in an attempt to grow the virus of inclusion blennorrhea. Thygeson<sup>6</sup> likewise was

<sup>6</sup> Thygeson P. Cultivation of Trachomatous Conjunctival Epithelium in Vitro, Arch Ophth 21 229 (Feb.) 1939

unable to propagate the virus on the chorioallantoic membrane of developing hen's eggs. It was hoped that a mutation of the virus might occur by serial passage of eggs already infected with the virus. The results were disappointing. Since there is no morphologic similarity between the tissue of the developing chick embryo and the conjunctival epithelium, one would expect the virus of inclusion blennorrhea to be easily adapted to the conjunctiva, however, it seems strange that the virus would not grow in tissue cultures of normal conjunctival epithelium. Undoubtedly, there is some change in the epithelial cells in tissue culture which makes them noninfective. It was suspected that some material was missing from the tissue culture, and since the supernatant fluid of the tissue culture could be varied, considerable variation was made in an attempt to propagate the virus by tissue culture.

The only changes in epithelial growth that could be obtained were with the addition of two amino acids, aminoacetic acid and histidine. The best growth of epithelium in tissue culture was obtained by the addition of small quantities of aminoacetic acid. Histidine and aminoacetic acid together seemed to be somewhat better, however, numerous essential amino acids were added to tissue culture in an effort to supply the missing substance which is present in the normal conjunctiva but not in the tissue culture.

The fate of the virus after inoculation either into eggs or tissue culture is difficult to understand, for, regardless of the type of medium into which it was placed, the virus disappeared quickly. It has been found from previous experience that the virus must be transferred carefully and quickly from the patient to the conjunctiva of baboons in order to obtain a good experimental inclusion blennorrhea. Since so many epidemics of so-called swimming pool conjunctivitis have occurred, it seems likely that the virus might live longer in distilled water or tap water than in isotonic sodium chloride solution U S P. Therefore the virus was suspended in sterile distilled water and inoculated into eggs, tissue culture and mice, but with disappointing results.

The negative results of inoculation in epithelial growth in tissue culture is a little easier to explain, the leukocytes present in the tissue probably destroyed the virus as it escaped from the cells, so that in a short time the organism disappeared. This may play a part in the rapid deterioration of the virus once it is suspended in any medium. If the virus of inclusion blennorrhea could be obtained free from leukocytes, perhaps it would grow in tissue culture.

#### BLIND PASSAGE IN MICE

In a further attempt to propagate the virus of inclusion blennorrhea, blind passage of material was made in mice. The method of propagation of a virus by blind passage has been fairly widely used, especially when the virus is not easily adapted to a new medium. In many cases

in which a large amount of infected material can be injected into a nonreceptive tissue, it may be possible to adapt the virus to the new cell. It is often possible to adapt bacteria to a new medium by continual transfer, though sometimes the organism loses some of its virulence in such passage. Because of the difficulty in adapting the virus of inclusion blennorrhoea to any medium except the cervix and

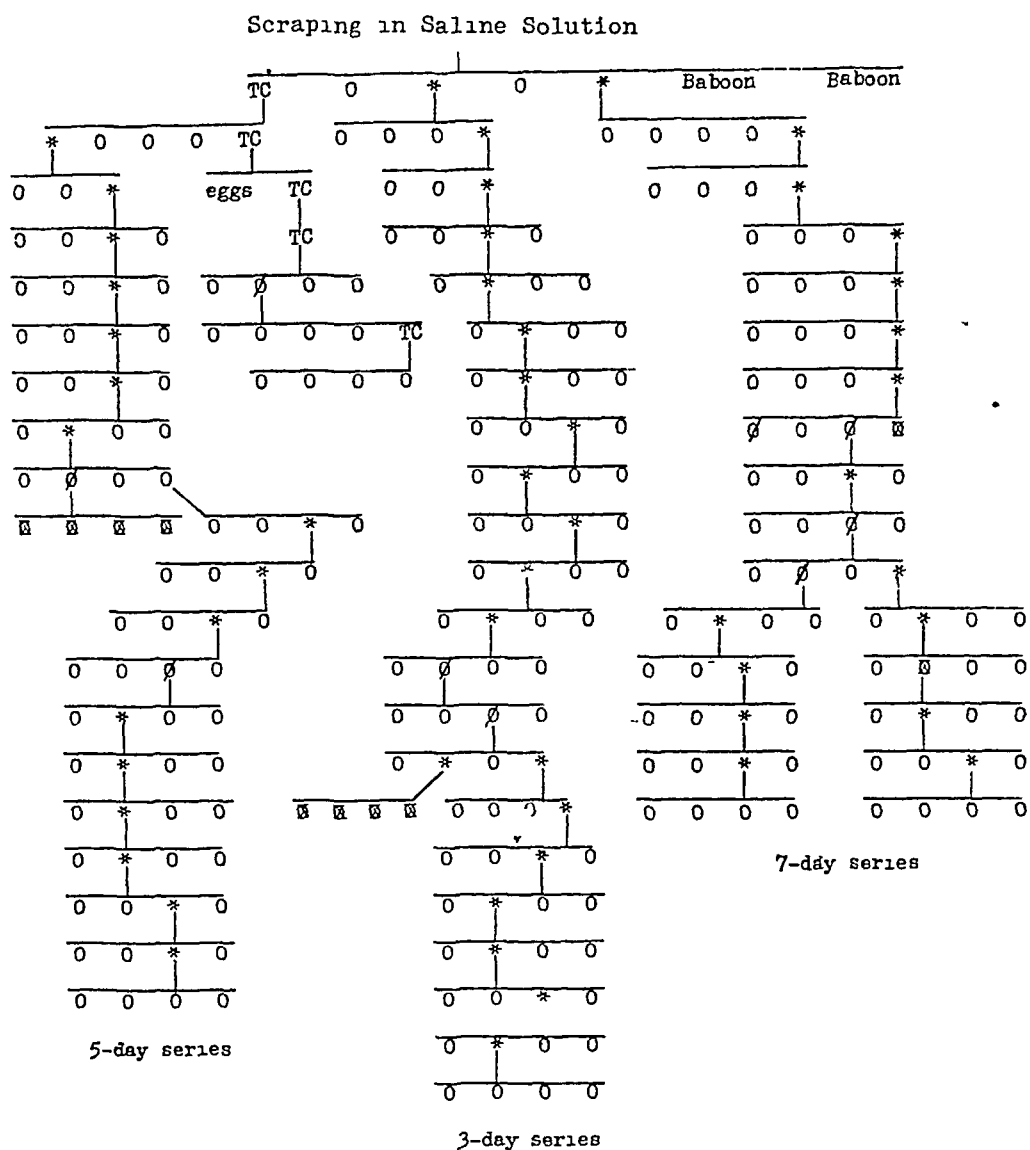


Chart 1—Passage through mice of the inclusion blennorrhoea virus from case 2

In this chart and in charts 2 to 8, 0 means mouse watched but not passed, 0 with included cross, mouse dead, 0 with one line, mouse sick and passed, and \*, mouse passed and not sick

the eyes of baboons, it was thought that with a heavy suspension of material obtained from the human eye under sterile conditions the virus could be adapted to mouse brain by serial passage. The mice used for blind passage weighed approximately 10 to 12 Gm

When the amount of solution was sufficient, from 3 to 5 mice were each inoculated intracerebrally, intraperitoneally and intravenously, as previously



In the first instance, an agent was found after four passages in the five day group. The potency of this agent could not be increased beyond 1 to 10 dilutions with isotonic sodium chloride solution U S P , and the agent eventually lost its potency and did not bring down mice after the tenth passage

In 1 instance, a good deal of material was obtained from the baby and suspended in a small amount of sterile neutral broth, this was

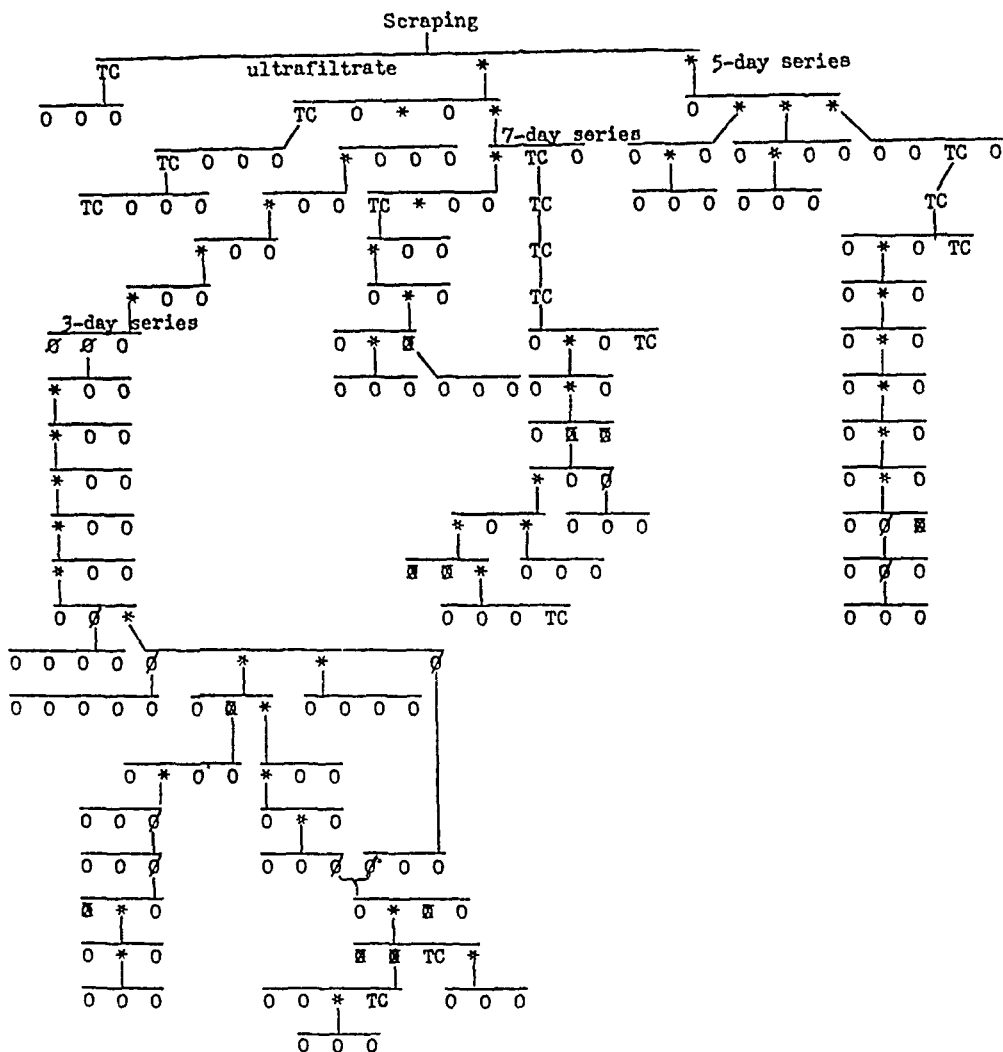


Chart 3—Passage through mice of inclusion blennorrhoea virus from case 4

injected intracerebrally into 3 mice and passage made after incubation for three days. After the fourth blind passage, an agent was obtained which had an incubation period of five days. Passage of this material was made at four day intervals, and the potency gradually increased until a dilution of  $10^{-6}$  was reached, which brought down all mice inoculated. This agent was considered as possible virus of inclusion blennorrhoea (chart 8). On continued passage, this agent maintained a potency up to  $10^{-6}$  and occasionally brought down mice in dilutions

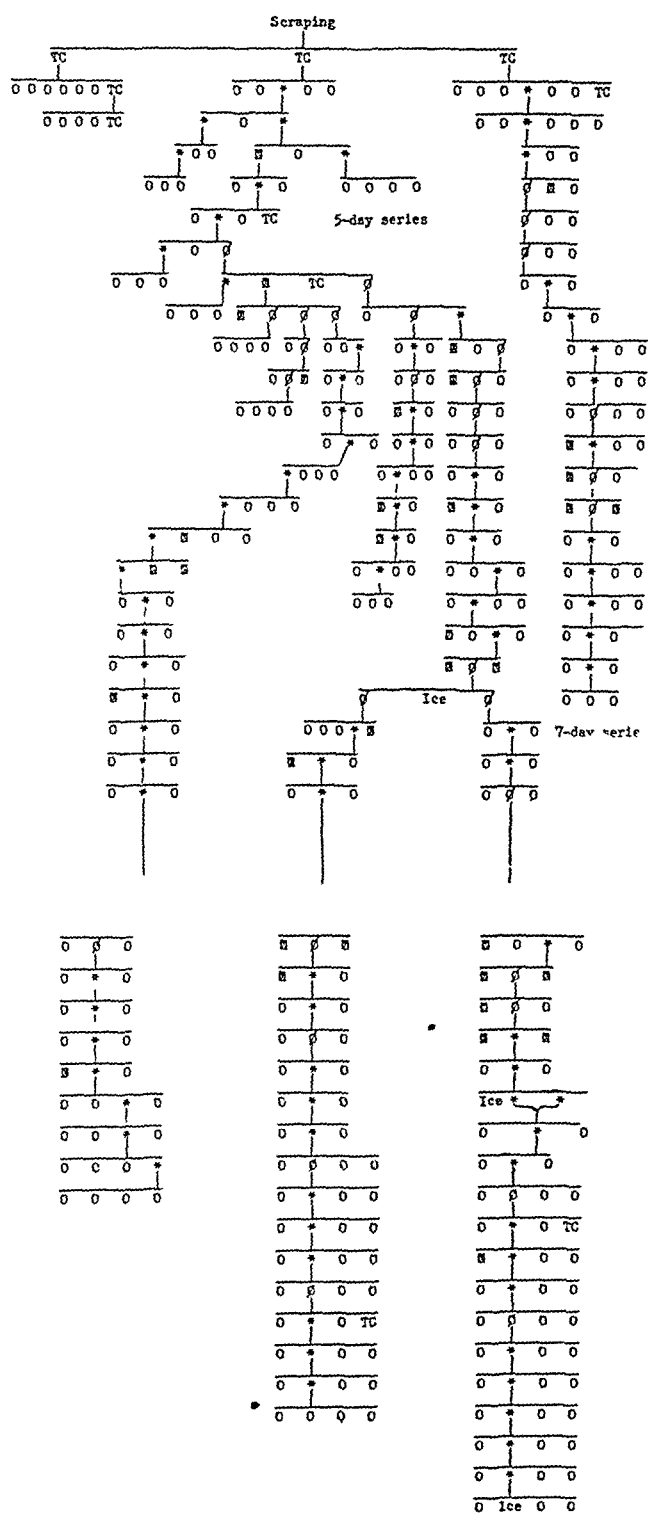


Chart 4—Passage through mice of inclusion blennorrhoea virus from case 5-T

of  $10^{-7}$  Because of the possibility of this being the causative agent of inclusion blennorrhea, many smears were made of the mouse brain. No inclusion bodies were demonstrated, and there was no evidence of a virus being present in the smears. The smear preparations were stained with Victoria blue and methyl blue and by the Giemsa method

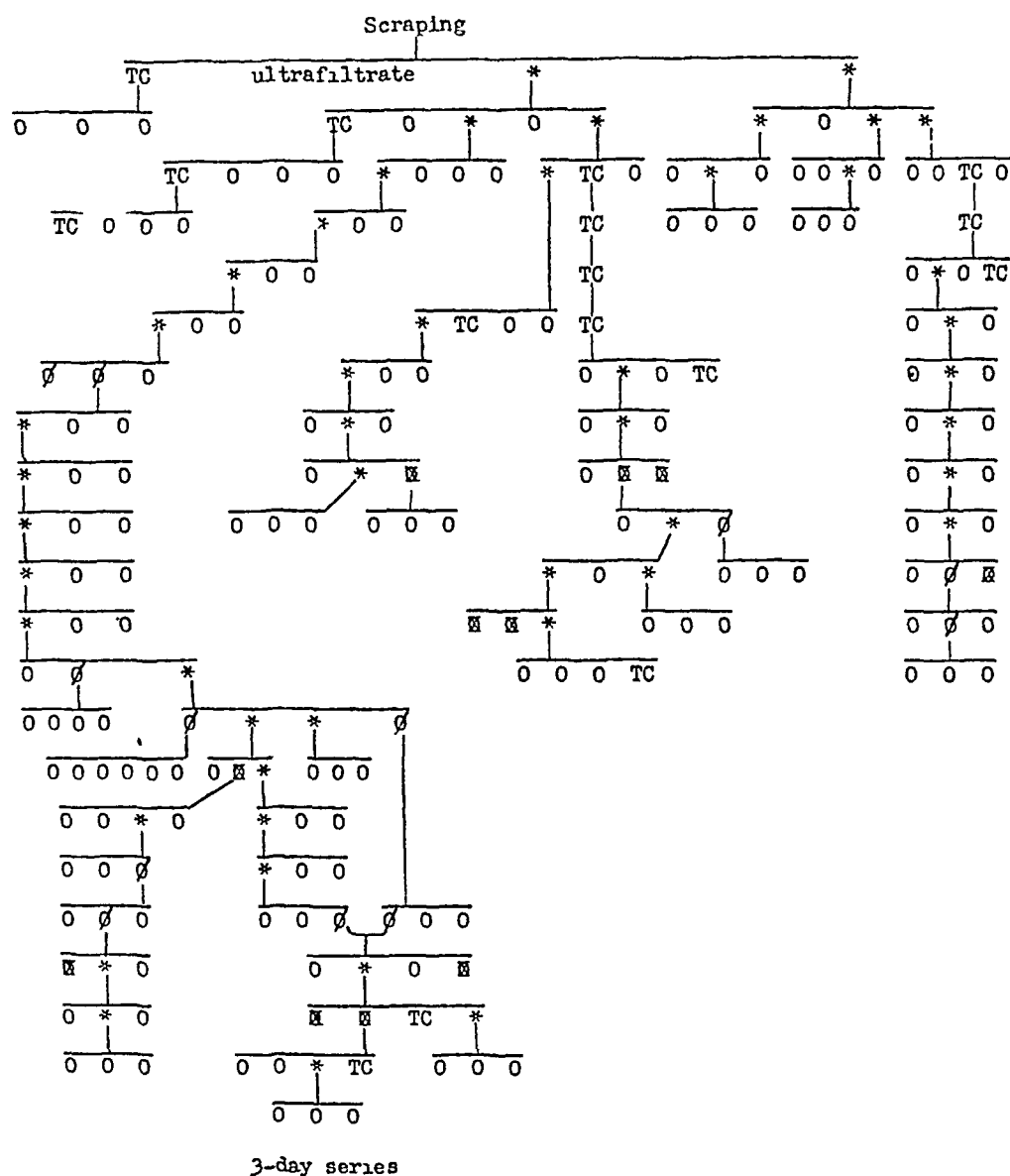


Chart 5—Passage of material from case 4-H

In a few smears stained with Victoria blue, some bodies were encountered, but these were thought to be artefacts. Since the agent had presumably been obtained from a patient with many free elementary bodies, it would seem proper that smears of the mouse brain should show elementary bodies. Mouse brain material suspended in isotonic sodium chloride solution USP and inoculated into the conjunctiva of dog-faced baboons gave rise to conjunctivitis in the baboons which

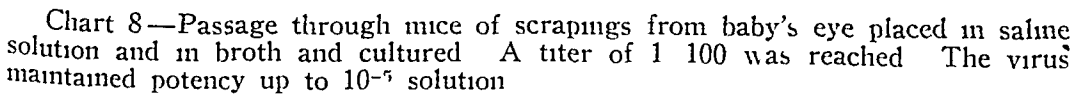




3



Scrapings from Baby's Eyes Placed in.



## NEUTRALIZATION TESTS

Since it was possible that a known virus had accidentally been recovered, cross neutralization with virus immune serums was carried out. Antiherpes serum was mixed with the agent and inoculated on the chorioallantoic membrane. The herpes virus gives rise to a typical lesion on the chorioallantoic membrane of the developing hen's egg. When the virus is mixed with antiserum, these typical lesions do not develop. There was no evidence of neutralization with antiherpes serum to the virus of inclusion blennorrhoea (table 2).

The possibility of infection with Theiler's virus was considered, since this virus is often present in mice and can be brought out by inoculation of sterile broth into the mouse brain. Although the mice used for experimental purposes were known to be free of this infection, Theiler immune serum was obtained in an attempt to neutralize our agent. The Theiler immune serum neutralized Theiler's virus up to  $10^{-2}$  but with our agent neutralization with Theiler's immune serum could not be obtained. The potency of the Theiler virus which was

TABLE 2—*Inclusion Blennorrhoea Virus with Antiserums for Three Viruses*

Theller	Negative, no protection
Lymphocytic choriomeningitis	Negative, no protection
Herpes simplex	Negative, no protection

used for experimental purposes was relatively low and could not be increased beyond  $10^{-4}$ . The agent was definitely not Theiler's virus.

Since the virus of lymphocytic choriomeningitis may have been a contaminant, an immune serum was made which prevented infection in the mouse brain with this virus. However, this immune serum did not protect the mice against our agent. It was thought, therefore, that the agent obtained was not the virus of lymphocytic choriomeningitis.

The original material was obtained from an infant, and it was not possible to obtain blood serum from the patient until a year and a half after the child had had the infection. In spite of this length of time, some indication of neutralization of the virus was obtained. Controls brought down mice in dilutions up to  $10^{-7}$  and, when mixed with the baby's serum brought down mice in dilutions up to  $10^{-5}$ . This would seem to indicate that the baby's serum had a trace of antibodies. Rabbits were immunized to the virus by intravenous injection of a small amount of live virus. After a period of six weeks, their blood contained neutralizing substances which would completely neutralize the virus. This substance was mixed with known viruses but showed no neutralizing power (table 3).

Serum was obtained from an adult with inclusion blennorrhea during the time that he had the infection. There was no evidence of neutralization of the agent. This fact, however, does not rule out the possibility that I may have been dealing with a virus-like inclusion blennorrhea, for it is known that in the case of the virus isolated from epidemic keratoconjunctivitis from two to three months is required for demonstrable immune bodies to be present in the blood serum. The known viruses that occur in mice are relatively small, usually in the neighborhood of 50 millimicrons. The virus of inclusion blennorrhea is considered to be more than 250 millimicrons, therefore, it would seem that filtration experiments should have given a lead as to the type of agent being dealt with. The virus of inclusion blennorrhea was difficult to filter through any of the candle type filters. It went through the Seitz filter without difficulty and maintained its potency. A series of Elford colloidin membranes were made. These were tested

TABLE 3—*Blood of Rabbits Immunized to Inclusion Blennorrhea Virus Against Following Viruses*

	Inclusion Blennorrhea	10,000, Neutralizing Dose
Theiler		0
Vaccinia		0
Lymphocytic choriomeningitis		0
Lymphogranuloma venereum		0
Herpes simplex		0

by the usual method, and membranes were obtained with an average pore size of 500 to 50 millimicrons.

#### FILTRATION EXPERIMENTS

The filtration experiments with the gradocoll filter (a graded colloidin membrane with an average pore of diameter of 0.6 micron) were somewhat disappointing because the virus passed filters with an average pore size of from 250 to 500 millimicrons and was retained by filters below 250 millimicrons. Therefore, we assumed that the virus measured between 100 and 200 millimicrons and was at the edge of visibility with the microscope. The agent passed through the Berkefeld V filter but did not pass the Berkefeld W filter. The virus also passed the Chamberland L5 filter as well as the Seitz filter (tables 4 and 5).

#### STAINING EXPERIMENTS

Numerous smears, sections and touch preparations were made from the brain, lungs, nasal cavity, spleen, liver, peritoneum and blood. These were stained by the Giemsa method and with Victoria blue, iodine, aqueous methylene blue, copper sulfate, methylrosaniline U S P

and phosphotungstic acid as well as for acid-fast bacilli. Many of these stains were used in the hope that the stain would be absorbed by the virus, thereby increasing its size enough to be visible with the microscope. No definite virus could be demonstrated, although in both sections and smears bodies were seen that appeared to be elementary bodies, particularly in the phosphotungstic acid preparations. With this stain it requires considerable judgment on the part of the observer to distinguish between cell granules and elementary bodies. The virus may have been visible, but, because of the confusion with the numerous normal cell granules that are stained by several of the methods used, it was thought advisable to conclude that the virus was

TABLE 4—*Ultrafiltration of Virus from Tissue Culture—Original Potency 10<sup>-2</sup>*

	Average Pore Size of Membrane, Millimicrons	Effect on Mice	
		Dead	Inoculated
	500 860		4 4
	500 600		4 4
	300 400		4 4
	250 300		3 4
	200 250		1 4
	175 200		1 4
	150 175		0 4

TABLE 5—*Filtration Through Other Filters*

	Average Pore Size of Membrane, Millimicrons	Effect on Mice	
		Dead	Inoculated
Seltz			4 4
Chamberland 5			4 4
Berkefeld V			4 4
Berkefeld W			0 4

not demonstrated in stained preparations. There is no doubt that the virus obtained was in no way like the virus of inclusion blennorrhea as it occurs in the human conjunctiva. The elementary bodies and initial bodies are easily seen and are not confused with normal cell granules. The same is true for touch preparations made from mouse brain inoculated with lymphogranuloma venereum. The elementary bodies and initial bodies are easily defined from normal cell granules. The only conclusion that can be reached from the stained preparations is that the agent was not the virus of inclusion blennorrhea, but another virus which could not be identified.

Another means of checking the agent obtained to determine whether it was the virus of inclusion blennorrhea was its sensitivity to sulfonamide drugs. The standard procedure used was to feed sulfanilamide

and sulfadiazine to mice for three days prior to inoculation. The mice were therefore fed sulfonamide drugs in their food, according to the procedure used by Marshall.<sup>7</sup>

Serial dilutions were then given intracerebrally in the mice. There was no appreciable protection against the virus with either sulfanilamide or sulfadiazine, though the incubation period, which was normally three to four days, was extended to seven to ten days after the use of either of the drugs. However, mice died in the same numbers as in the control series.

Since we had obtained an overwhelming infection in mice that caused death within a week, we thought that the spleen, liver or lungs of the mice might give us a lead. The spleens and livers removed from the

TABLE 6—*Distribution of Inclusion Blennorrhoea Virus in Mice*

Route of Injection	Brain	Liver	Spleen	Lungs	Blood
Intracerebral	10 <sup>-7</sup>	10 <sup>-6</sup>	10 <sup>-4</sup>	Negative	10 <sup>-1</sup>
Intraperitoneal	10 <sup>-1</sup>	10 <sup>-1</sup>	10 <sup>-3</sup>	Negative	10 <sup>-3</sup>
Intravenous	10 <sup>-6</sup>	10 <sup>-5</sup>	10 <sup>-4</sup>	Negative	10 <sup>-2</sup>
Intranasal	Negative	Negative	Negative	Negative	Negative
Feeding by mouth	10 <sup>-3</sup>	10 <sup>-2</sup>	10 <sup>-2</sup>	Negative	Negative

TABLE 7—*Pathogenicity for Other Animals*

	Cornea	Conjunctiva	Intracerebral	Intraperitoneal
Rabbit	Negative	Negative	10 <sup>-1</sup> (2 of 4 dead)	Negative
Guinea pig	Negative	Negative	Doubtful (1 of 5 dead)	Negative
Monkey	Negative	Doubtful	10 <sup>-1</sup> (1 of 2 dead)	Negative
Baboon	Negative	Follicular	10 <sup>-1</sup> Possible	Negative

mice were infectious on intracerebral inoculation of other mice. Smears of the liver and spleen failed to demonstrate any evidence of the virus. The lungs were noninfectious. Blood removed from the hearts of mice which died of the virus was also noninfectious when injected intracerebrally in other mice (table 6).

The virus was only moderately pathogenic when injected intracerebrally in rabbits and guinea pigs, however, the incubation period in both rabbits and guinea pigs was somewhat prolonged. The rabbits, however, formed antibodies to the virus if they survived. Rabbits were given a suspension of mouse brain and virus intravenously, and there developed a high degree of protective substances in their blood when it was mixed with the virus and injected intracerebrally in mice (table 7).

<sup>7</sup> Marshall, E. K., Jr. *Physiol Rev* **19** 240 (April) 1939.

The virus was attenuated if kept in a water bath at 60 C for one hour. It killed 2 to 6 mice when injected with dilutions of  $10^{-1}$ . Control mice in this series were all dead. The virus was apparently killed at 70 C for one hour, for there were no deaths in 6 mice when the virus was injected in the same dilutions. The virus was also killed if heated at 60 C for two hours.

The virus kept in the ice box remained active for two months, and it maintained its activity for three weeks in 50 per cent glycerin.

Since the virus could be grown well in tissue culture and remained infectious, I tested its growth in a tissue culture mixture which contained no living cells. The tissue culture was made of serum ultrafiltrate and balanced saline solution with finely divided embryonic mouse brain. With this culture the virus grew and increased in potency. If the embryonic mouse brain was omitted from the tissue culture, leaving only balanced saline solution and serum ultrafiltrate, the virus quickly died and became noninfectious.

The virus maintained its potency when kept frozen at  $-60^{\circ}\text{C}$ . It also maintained its potency for a period of six months after being completely dried in the lyophil apparatus.

After the virus was established, it could be passed intracerebrally, intravenously or intraperitoneally but could not be passed to mice by the intranasal or the oral route. Occasionally mice came down when they were fed the virus by mouth, however, this was not a particularly good method of inoculation.

All mice were susceptible regardless of size and age, and we were unable to develop an immune strain of mice by repeated inoculations of small amounts of the virus in high dilutions. Heavy suspensions of the virus were inoculated on the cornea of rabbits but produced no effect.

Attempts at digestion of the virus with pneumococcus enzyme and pepsin had little or no effect on the potency of the virus.

#### ATTEMPTS TO REPRODUCE THE DISEASE

Mouse brain material used in serial passage in mice was suspended in isotonic sodium chloride solution U S P and inoculated on the conjunctiva of the baboon. Several drops of the infected material were rubbed onto the conjunctival sac of the baboon with a sterile cotton swab. The conjunctiva was watched for the development of conjunctivitis. With one of the agents, conjunctivitis was repeatedly obtained in baboons. The baboon would recover from the conjunctivitis in from two to six weeks. While the baboon had conjunctivitis, the tarsus of the upper lid and the retrotarsal fold of the lower and upper lids were covered with large follicles. This was associated with a slightly purulent discharge. Occasionally a small amount of edema was present in the upper lid. Epithelial scrapings from the conjunctiva repeatedly

failed to show inclusion bodies After a period of approximately three months, these baboons were again inoculated with material obtained directly from babies with inclusion blennorrhea Conjunctivitis did not develop in these animals, whereas in baboons which had previously been inoculated with inclusion blennorrhea virus from a baby or had never been inoculated with any virus inclusion blennorrhea developed The baboons inoculated with inclusion blennorrhea virus 5 were entirely immune to further inoculation with inclusion blennorrhea from patients There is no doubt that the virus which was so potent in mice gave rise to conjunctivitis in the baboon The conjunctivitis, however, was not typical experimental blennorrhea The conjunctivitis produced was a follicular type, similar to the spontaneous follicular conjunctivitis that sometimes occurs in baboons Trauma to the lids may have produced some of the conjunctivitis, but this should have disappeared in a short time

From past experience, it is known that the baboon does not maintain an immunity to inclusion blennorrhea after it has recovered from the disease If material from the eye of a baby or an adult with inclusion blennorrhea is inoculated on the conjunctiva of a baboon, the result is a moderately severe follicular conjunctivitis, which lasts from one to two months After the attack the baboon's eye can again be inoculated with material from an eye with inclusion blennorrhea and conjunctivitis is again produced, entirely similar to the first It is doubtful, then, whether any immunity is developed by inoculation with material from inclusion blennorrhea

Since the baboons were inoculated with a potent virus and exhibited a follicular conjunctivitis but an experimental inclusion blennorrhea failed to develop when they were inoculated with inclusion blennorrhea, the results can be explained by the so-called interference phenomenon, in which one virus will produce antibodies which are reasonably nonspecific and give some degree of protection against other viruses This is especially true of the interference between herpes and vaccinia, since the inoculation with vaccinia will interfere with the development of herpes in the rabbit

The experiment was repeated on 8 different eyes, and all the baboons showed an immunity to inclusion blennorrhea after having first been inoculated with the virus

#### GENERAL COMMENT

The viruses of psittacosis, lymphogranuloma, trachoma and inclusion blennorrhea are morphologically similar The viruses of psittacosis and lymphogranuloma grow well in an endothelial type of tissue, while the viruses of trachoma and inclusion blennorrhea seem to require



conjunctival epithelium in order to reproduce. The viruses of lymphogranuloma and psittacosis have both been adapted to the mouse brain though often repeated passages of lymphogranuloma material are required finally to produce adaptation of the virus to the mouse brain. Once it is adapted, however, it grows well and can be studied easily. When the virus of lymphogranuloma is grown in mouse brain, smears of the brain usually reveal large numbers of elementary bodies. It would seem that if the virus of inclusion blennorrhoea could be grown in the mouse brain it would likewise show large numbers of inclusion and elementary bodies on smears of mouse brain. However, repeated smears of virus obtained from the mice inoculated with inclusion blennorrhoea did not demonstrate elementary or inclusion bodies. It was therefore assumed that the virus was changed so completely that it would not stain by the Giemsa method. On filtration experiments with the virus of inclusion blennorrhoea with gradocoll filters, the virus should have been visible in the microscope, and the infectivity for the mice was so high that there should have been quantities of virus material on the stained smears. Other stains were used to identify the material, and with the phosphotungstic acid stain bodies were observed which simulated elementary bodies. The phosphotungstic acid stain, however, was so confusing in smear preparations that it was impossible to tell the elementary bodies from the cell granules.

#### CONCLUSION

It can be assumed that a new, unknown virus was isolated, however, it may represent a variant of the virus of inclusion blennorrhoea. The psittacosis group of viruses, in their natural form, stain like bacteria. On the whole, their pathogenic activity is more like a moderately virulent bacterium than like a virus. Their requirements for multiplication are, however, those of a typical virus. Burnet<sup>8</sup> has shown that mutation occurs in virus diseases. This is considered true of the influenza virus, of which types A, B and C are examples.

In the manner in which the virus of inclusion blennorrhoea was handled in passing through the mouse brain, it is quite possible that a mutation of the inclusion blennorrhoea virus may have occurred, transforming an atypical virus into a typical one. This could explain all the seemingly peculiar experimental data presented here.

If one can assume that the unknown virus which I present is a variant of the virus of inclusion blennorrhoea, one can say that it has been transformed into a true virus. This virus, then, could give rise to a

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8 Burnet, F. M. *Virus as Organism: Evolutionary and Ecological Aspects of Some Human Virus Diseases* (the Edward K. Dunham Lectures for the Promotion of the Medical Sciences), Harvard Monographs in Medicine and Public Health, no. 8. Cambridge, Mass., Harvard University Press, 1945.

follicular conjunctivitis in baboons in which there might be immunity to further inoculation with the virus of inclusion blennorrhoea from a patient. The patient's serum carried antibodies to the virus about a year after the original infection, even though they were low in potency. This assumption would also explain the large filtration size of the virus, the difficulty in staining and the development of antibodies in rabbits and baboons. If viruses are considered a mutation from bacteria by loss of their ability to synthesize artificial mediums, it appears highly probable that a mutation of an atypical virus could be brought about. Beadle<sup>9</sup> and his collaborators, working on a mold, *Neurospora*, which grows on almost anything, found that by treating this mold with roentgen radiation variants were produced which required a complex medium for growth. These investigators produced over two hundred such variants. Although there is considerable difference between this mold and the viruses of the psittacosis group, one may consider that all four diseases may represent variants of the original virus. Since this group is closely related in some respects to bacteria, e g, in staining properties and in sensitivity to the sulfonamide drugs, and in other respects to viruses, variants could have occurred.

It is therefore concluded that the virus of inclusion blennorrhoea as it occurs in the human eye was not grown, but that a variant which was a true virus was produced from the atypical virus of inclusion blennorrhoea.

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<sup>9</sup> Beadle, G. W., and Tatum, E. L. Proc. Nat. Acad. Sc. **27** 499 (Nov.) 1941.

# USE OF PHENYLEPHRINE HYDROCHLORIDE (NEO-SYNEPHRINE HYDROCHLORIDE®) IN OPHTHALMOLOGY

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THE FIRST studies on the ocular use of phenylephrine hydrochloride (neo-synephrine hydrochloride®) were begun in 1933 and reported in 1936<sup>1</sup> Since then, extensive clinical experiences with this drug have accumulated with additional observations The object of this article is to review these data, bringing them up to date

Phenylephrine hydrochloride (laevo- $\alpha$ -hydroxy- $\beta$ -methylamino-3-hydroxyethylbenzene hydrochloride) is the salt of the laevo isomer of a synthetically prepared derivative of phenylethylamine It is a white, crystalline, nonhygroscopic compound, readily soluble in water and alcohol It is relatively stable The melting point ranges from 138 to 142 C

Pharmacologically, phenylephrine belongs to the group of compounds possessing sympathomimetic activity It is an active vasoconstrictor agent when given either orally or parenterally As a vasoconstrictor, it has the desirable quality of rarely causing any compensatory dilatation Phenylephrine relaxes the sphincter muscle of the iris and strongly contracts the radial fibers This characteristic, together with its pronounced decongestive action, makes it valuable to the ophthalmologist Occasionally light cycloplegia is observed after topical application of the 10 per cent preparations The lowering of intraocular pressure from the use of this compound is not constant, and in this role it is like epinephrine Isolated and in situ studies of the effects of sympathomimetic compounds on the iris are well known Conclusive studies on the epinephrine-like compounds and their precise effects on the ciliary ring are not known to have been reported (Subconjunctival injections of phenylephrine do not enhance its effectiveness)

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1 (a) Heath, P Neosynephrine Hydrochloride Some Uses and Effects in *Ophthalmology*, *Arch Ophth* **16** 839 (Nov) 1936 (b) Post, W L Neosynephrine, *Am J Ophth* **20** 170 (Feb) 1937 (c) Heath, P, and Geiter, C W Some Physiologic and Pharmacologic Reactions of Isolated Iris Muscles, *Arch Ophth* **21** 35 (Jan) 1939

Primarily, solutions of phenylephrine hydrochloride in the 2.5 and 10 per cent solutions contained ascorbic acid. This substance is a powerful reducing agent, and, while it was a great aid in preventing oxidation of the phenylephrine, after a short time in solution it produced an amber discoloration. However, the chief undesirability of ascorbic acid was due to its lowering of the  $p_H$ , causing stinging, and also preliminary congestion, on topical application. The new solutions do not contain ascorbic acid but do contain a buffering agent, which stabilizes the  $p_H$  and greatly reduces the irritation.

Solutions for ophthalmic preparations should possess certain specific characteristics when possible. The ideal range of the  $p_H$  is from 7.0 to 7.6, although solutions with a lower  $p_H$  do not necessarily cause stinging. Irritation may be of benefit if vasodilation goes with it, and is in itself beneficial, or harmful, if dilution from tearing results. Ophthalmic solutions should be adjusted so that their isotonicity is within the range of a 1.0 to 1.4 per cent solution of sodium chloride, the higher percentage being equivalent in isotonicity to that of tears (1.32 to 1.427). The isotonicity is usually determined by the freezing point. While the optimum gravity for ophthalmic solutions is suggested as 1.004 to 1.005, it is not clearly understood just what part this factor plays. The range apparently is wide, since our experiments have shown considerable latitude. Some ophthalmic solutions should contain wetting agents. Primarily, the basic medication should be capable of penetrating the cornea and be compatible with the wetting agent, otherwise, the addition of this agent is of little value. Local irritation from a medical preparation is of decided secondary importance to achieving effective concentration of the medicament at the suitable point of action. If possible, the vehicle for the ophthalmic drug should be self sterilizing.

Since one of us (P. H.)<sup>2</sup> introduced one of the first low tension ophthalmic preparations in the form of an oil-in-water emulsion, many wetting agents have been suggested and used. Bellows and Chinn, Gifford, and O'Brien and Swan have demonstrated that the use of wetting agents definitely enhances the penetrability of many useful ophthalmic drugs. However, even with the recent advances in pharmaceutical chemistry, it is impossible in many instances to prepare certain drugs within the range of the previously mentioned specifications for an ideal ophthalmic preparation. This is true because the stability of the different commonly used drugs varies according to the  $p_H$  of the solution, as Gifford has pointed out. Some high percentage solutions

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<sup>2</sup> Heath, P. Use of Emulsions in Ophthalmology, *Am J Ophth* **22** 904 (Aug) 1939

have a greater tendency to produce undesirable irritation in spite of their other component pharmaceutical perfections. For example, 1 Gm of phenylephrine hydrochloride is equivalent in isotonic properties to 0.28 Gm of sodium chloride.<sup>3</sup> The 2.5 per cent solution is approximately isotonic (equivalent to 1.2 per cent sodium chloride solution) with the preservatives, wetting agent (0.001 per cent aerosol OT 100 per cent, or sodium dioctylsulfosuccinate) and buffer added. With 10 per cent it is impossible to make an isotonic solution, because in this concentration it would be equivalent to at least a 2.8 per cent solution of sodium chloride. With the other necessary salts added, its isotonicity is approximately equivalent to that of 3.3 per cent sodium chloride solution, which causes some pain unless a topical anesthetic is used first. In contrast to this, the 10 per cent emulsion is not nearly so irritating, a characteristic which is due in part to the emollient effect of the oil content.

#### CLINICAL USES OF PHENYLEPHRINE HYDROCHLORIDE

1 As a decongestive agent, for use in mild conjunctivitis, the prescription may contain 0.0125 per cent phenylephrine hydrochloride in association with other drugs. It should not be used indefinitely. To produce a substantial decongestion of the globe, one may use a 10 per cent emulsion or a 10 per cent solution, instilled after the use of a topical anesthetic. After application of the emulsion, dry particles of acacia (part of the emulsion base) may be observed on the lid margins. These are readily removed with moistened cotton.

2 Phenylephrine hydrochloride may be used as a mydriatic for the following purposes: (a) In examination of the fundus. The best prescription for this use is a 2.5 per cent solution dropped once or twice in the eyes, for more rapid dilation a drop is applied every five minutes three or four times.

(b) In breaking adhesions of the iris to the lens (sometimes to the cornea). For this purpose, it is best to apply the 10 per cent emulsion to the upper portion of the cornea, after preliminary instillation of 1 drop of a topical anesthetic and an interval of two minutes. Sometimes the use of atropine contracts the pupil partially after the use of the phenylephrine. The interval of dilatation following instillation of the stronger solution varies from two to six hours.

(c) In refraction, especially in cases of presbyopia and myopia. This enables one to obtain an objective measurement with the shadow

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<sup>3</sup> Welles, J. Calculating Isotonic Solutions, *J. Am. Pharm. A.* 5:99 (April) 1944.

test, as well as to examine the fundus by ophthalmoscopy. Higher errors of both sphere and cylinder, overlooked by subjective testing, may be derived through objective examination. A 2.5 to 5 per cent solution is used.

(*d*) In cycloplegia. When the iris is resistant to dilation with the usual cycloplegic, although one may have paralysis of the ciliary body, the addition of phenylephrine will often produce a wider dilatation of the pupil.

(*e*) In overcoming extreme miosis in glaucoma. It may be used with miotics. Its decongestive effect is valuable, especially in cases of glaucoma of the shallow anterior chamber type (Sugar<sup>4</sup>), and its prolongation of the effect of the miotic is also useful. Furthermore, it reduces the difficulties experienced by the patient because of the small field, due to the extremely narrowed pupil, and still permits, and often supports, the effect of the miotic in lowering the intraocular pressure. Post<sup>1b</sup> reported using phenylephrine with physostigmine. If the increased intraocular pressure is based on a mechanical blockage of the angle, it is important to avoid a solution of phenylephrine of sufficient concentration to bring about this hazard. Experience from trial with weak solutions, from 0.25 to 1.0 per cent and upward, will give the desired information on the action of the drug.

(*f*) In beginning intraocular operation when one wishes to have the benefit of a widely dilated pupil at the time of operation and then to have the pupil contract shortly thereafter. It is useful in cases in which a needling is to be performed for secondary cataract operation and in cataract operations in general, and even in cases of increased intraocular pressure or borderline pressure. The dilatation facilitates the removal of the lens, and postoperative contraction of the pupil may be induced by miotics. A 2.5 per cent solution, to be repeated, or a 5 per cent solution given once, is the best prescription.

(*g*) In provocative testing for glaucoma induced by dilated pupils. A rapid miosis may be readily induced with the usual miotics.

(*h*) As a supplement to a mydriatic when there is sensitivity to the mydriatic used.

3. This compound is of great value in infiltration anesthesia, both for major and minor surgery, for the following reasons: (*a*) The drug acts as a decongestive, (*b*) prolonged action of the infiltration anesthesia is maintained, (*c*) there is slower absorption, (*d*) the drug is an antispasmodic, (*e*) there are few or no side reactions. The best prepa-

<sup>4</sup> Sugar, H. S. Acute Glaucoma. A Follow-Up Study. *Am. J. Ophth.* 30:451 (April) 1947.

ration for this purpose is a 1 per cent sterile solution. This is used in a proportion of 0.3 to 0.5 cc of 1 per cent sterile solution to 10 cc of anesthetic solution (1:3,333 to 1:2,000).

4 Its use with application of cold in the reduction of edema and congestion in the allergic form of acute conjunctivitis has been reported by Koch.<sup>5</sup>

5 Phenylephrine has been combined with sulfathiazole.<sup>6</sup> This salt in an 0.6 per cent solution is equivalent in vasoconstrictor action to the 0.25 per cent of the phenylephrine hydrochloride. It has a limited use in ophthalmology—the 0.6 per cent solution has bacteriostatic properties useful in cases of obstinate blepharitis.<sup>7</sup>

6 Phenylephrine hydrochloride, 0.25 per cent, has also been combined with tetracaine (pontocaine®) hydrochloride, 0.5 per cent, for ocular and nasal application to overcome pain and blepharospasm and to permit further treatment after exposure to irritating gases and “flash” burns in industrial medicine.

7 The hemodynamic properties of phenylephrine hydrochloride have been used clinically by Johnson<sup>8</sup> in cases of shock. The dose is 50 to 100 mg given subcutaneously or 3 mg given intravenously.

#### COMMENT

Rapid absorption of substantial amounts of phenylephrine causes marked and hazardous increase of the blood pressure. Systemic absorption through the anterior segment of the eye is slow and limited in degree. To investigate this, a study was made on 60 clinic patients and 60 private patients. This study included the measurements of the blood pressure and the intraocular pressure before instillation of phenylephrine into the eyes. These two measurements were then made one hour after the instillation of the drops. A variety of ophthalmic and general disease states were represented in each group of subjects, among them incipient glaucoma, aphakia, cataract, hypertension, renal disease, blood dyscrasias and diabetes. The blood pressure readings after use of phenylephrine were unaltered in about 40 per cent of the cases, lowered slightly in about 58 per cent and slightly increased in

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5 Koch, F. L. P. *Ophthalmological Expressions of Allergy, Eye, Ear, Nose & Throat Monthly* **23** 483 (Dec.) 1944.

6 Geiter, C. W., Lands, A. M., and Lewis, J. R. *A Study of a New Salt of Neosynephrine*, *J. Am. Pharm. A. (Scient. Ed.)* **33** 359 (Nov.) 1944.

7 Heath, P. *Chemotherapy in Ophthalmology*, *J. A. M. A.* **124** 152 (Jan. 15) 1944.

8 Johnson, C. A. *Study of Neo-Synephrine Hydrochloride in Treatment of Acute Shock from Trauma or Hemorrhage*, *Surg., Gynec. & Obst.* **63** 35 (July) 1936.

2 per cent A variation of  $\pm 4$  mm was designated as "no change" and a drop or rise, on the basis of 5 mm or over From this investigation it was concluded that no significant changes in either blood pressure or intraocular pressure were produced, this conclusion being subject to one qualification, namely, that in cases with narrowed angle, blockage from iris tissue can occur as the pupil is dilated, thus causing increased intraocular pressure

We have never noted or had reported any harmful effects on the ocular tissues or the blood vessels from the use of this substance Neither sensitivity nor delayed healing has been reported Phenylephrine hydrochloride has a wide range of uses and has firmly established its importance in ophthalmology as a valuable therapeutic and diagnostic substance

Massachusetts Eye and Ear Infirmary, Boston (Dr Heath)

North Kansas City (Route 4), Mo (Dr Geiter)



# JUXTAPAPILLARY HEMANGIOENDOTHELIOMA OF THE RETINA

• Report of a Case

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READING, PA

THE OCCURRENCE of hemangioendothelioma of the retina, or von Hippel's angiomatosis retinae, is frequent enough to be hardly worthy of special comment. The case which is presented, however, is sufficiently interesting and unusual to be brought to the attention of ophthalmologists.

## REPORT OF CASE

H S, a medical officer aged 40, white, was admitted to Dibble General Hospital on March 27, 1945, for investigation of blurred vision in the right eye of ten months' duration. This symptom was first observed when the patient noted that he could not focus with his right eye when using a pair of field glasses. His records indicated that in June 1943, prior to his departure overseas, vision was 20/25 in his right eye and 20/20 in his left eye with a mild correction for myopia. The patient showed no immediate concern over his newly discovered blurred vision in the right eye, but three months later, in October 1944, he visited the eye clinic of an overseas general hospital, where examination indicated the probability of "an exudative hemorrhagic lesion of the optic nerve." Visual acuity in the affected eye was 20/200, with correction, and no further study was conducted at that time. In February 1945 the patient was examined in the eye clinic of another overseas general hospital, where the possibility of a tuberculoma of the optic nerve or of retinochoroiditis juxtapapillaris was suggested. The patient was then returned to the United States on the basis of an ordinary leave, to visit his sick mother. On arriving in this country, he reported to a dispensary at Fort Mason, San Francisco, where an ophthalmologic examination disclosed what was thought to be a tumor of the optic nerve. The patient was then transferred to Dibble General Hospital for continued observation and treatment.

On his admission to this hospital, a complete physical examination indicated that the pathologic process was limited to the right eye. The past medical and family histories were essentially noncontributory.

The ophthalmologic examination revealed vision of 8/400, correctible to 20/300 with a -1.25 D sphere in the right eye and 20/50, correctible to 20/15 with a -1.25 D sphere in the left eye. No test letters on a Jaeger chart were visible at the near point with the right eye. Ability to read Jaeger test type 1 was recorded for the left eye.

External examination of the right eye showed full ocular rotations, normal intraocular tension on palpation and dilatation of the pupil, due to a mydriatic drug.

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Submitted for publication with the cooperation of the Army Institute of Pathology, Colonel Raymond O Dart, Medical Corps, United States Army, Director.

There was no exophthalmos, readings with the Hertel exophthalmometer indicating 16 mm for each eye. The left eye appeared normal. Examination with the slit lamp revealed no abnormality in the anterior segment of either eye.

Ophthalmoscopic examination of the right eye was reported as follows (fig 1). The media were clear. A large, round, orange mass was seen to arise from the temporal aspect of the disk and extend laterally toward the macula. The diameter of the lesion was estimated to be slightly more than 1 disk diameter, and its elevation, 25 D. Its surface presented a mottled effect, and moderate vascularity was apparent. The border showed a condensation of pigment. A portion of the tumor appeared to surround the superior temporal vein (not shown in the artist's conception of the tumor), and a number of large blood vessels were seen in the tumor, these vessels extended from the retinal circulation. The macular region appeared

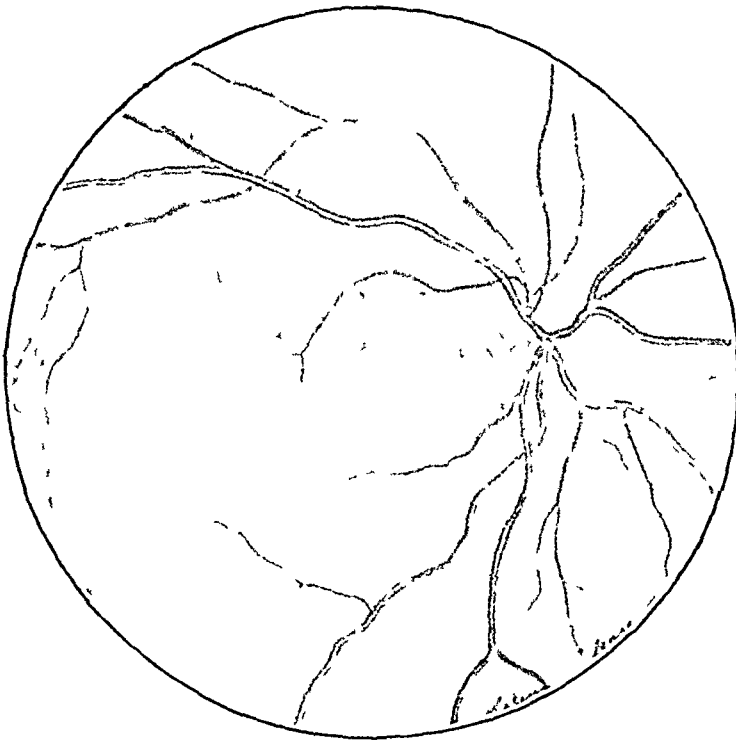


Fig 1—Hemangioendothelioma of the retina adjacent to the nerve head

somewhat elevated, the result of edema. The rest of the fundus appeared normal. The left eye was normal.

Examination of the central visual field was made shortly after the patient's admission to the hospital, unfortunately, the record of this examination could not be obtained for illustration. The examination revealed enlargement of the blind-spot and a central scotoma to red, which measured 5 degrees, was noted.

Roentgenographic studies of the skull and optic foramina were conducted, revealing a normal status. Blood studies and urinalysis also gave normal results. The patient was seen in consultation by Dr. Frederick C. Cordes, civilian consultant in ophthalmology of the Ninth Service Command, who corroborated the report. Dr. Cordes suggested the diagnostic possibility of perithelioma or of neuroepithelioma of the optic nerve. The patient's course in the hospital prior to enucleation was remarkable only for the improvement in visual acuity in the affected eye to 20/30, with correction, as determined on May 15, and examination of the central visual field at this time revealed a large pericentral scotoma which practically encircled the fixation point.

Ophthalmoscopic study at this time suggested increase in the area of the tumor, although there was no increase in its elevation. It was also believed that the surrounding retinal edema had diminished somewhat, a change which probably explained the improvement in visual acuity and the disappearance of the central scotoma originally observed. In spite of definite improvement in visual acuity, it was felt that the patient presented a malignant tumor of the right optic nerve, and enucleation was recommended.

Operation was performed on May 22. At the time of enucleation 2 cc of vitreous humor was aspirated through a scleral incision for use in a transplantation to another patient<sup>1</sup>. The eyeball was enucleated in the usual manner, and care was taken to obtain a long section of the optic nerve. The enucleated eye was replaced by a basket type acrylic implant, described by Cutler<sup>2</sup>.

Healing of the socket was uneventful, and a satisfactory acrylic prosthesis was ultimately fitted. The patient's general condition remained satisfactory throughout the period of observation, which continued until December 1945.

*Pathologic Study of the Eye* (Army Institute of Pathology, Director, Col J E Ash, Medical Corps) —The following report, dated July 11, 1945, was submitted by the Institute (fig 2)

"Gross Study. The specimen consisted of an eye measuring 25.5 by 24.5 mm. There was a sutured scar almost at the equator. The eye was opened in the horizontal plane. A small, opaque, elevated, granular lesion, about 2 mm in diameter, arose from the cupped optic disk and encroached on the retina, almost to the swollen macula. There was a posterior synechia.

"Microscopic Study. The cornea was not remarkable. The angle of filtration was clear. There were posterior synechias with a partial ectropion uveae. The ciliary processes showed more hyalinization than usual for one of the patient's age. The choroid was not remarkable. Some round cell infiltration was present about the posterior episcleral vessels, with a margination of polymorphonuclear leukocytes. Most of the lens substance was absent. The retina was detached, and anteriorly there was a very small hemorrhage. Some serous exudate lay beneath the macula anteriorly, where the latter was cystic. Arising apparently in the nerve fiber layer at the margin of the disk was a small tumor, made up of round and spindle cells, some of the former with a generous amount of cytoplasm, which was usually vacuolated. The tumor was highly vascular, the vessels were thin walled. The tumor had invaded the retina as far as the external limiting membrane and had extended onto the temporal half of the disk. Clusters of cells lay among the nerve fibers just outside the cribriform plate. These did not have quite the neoplastic character of the cells of the tumor. They probably represented reactive gliosis. The tumor extended in the nerve fiber and ganglion cell layers into the edge of the macula. There were large cystic spaces in the inner nuclear and outer plexiform layers of the macula. The tumor is interpreted as a glioma of the retina of mixed cell type, including oligodendroglia with a few astrocytes. It is not considered malignant. It is felt that the neoplasm has been entirely removed. Gross section of the optic nerve showed no tumor."

Additional study of the tumor by the Army Institute of Pathology led to the revised diagnosis of von Hippel's hemangiogliomatosis.

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1 Cutler, N L. Transplantation of Human Vitreous, *Arch Ophth* **35** 615 (June) 1946.

2 Cutler, N L. A Basket Type Implant for Use After Enucleation, *Arch Ophth* **35** 71 (Feb) 1946.

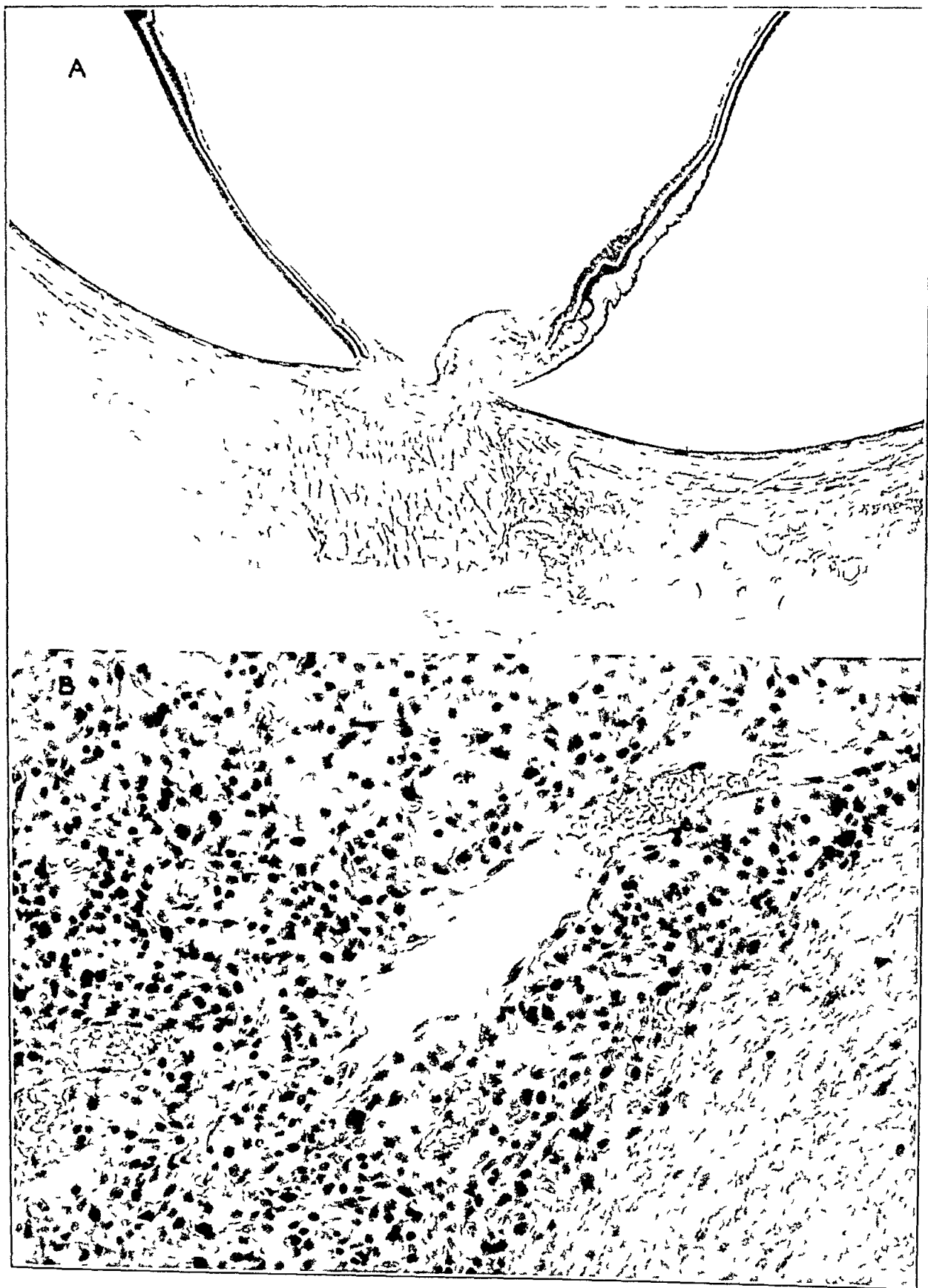


Fig 2—*A*, well circumscribed tumor, a hemangioendothelioma of the retina,  $\times 11$  Army Institute of Pathology, negative 103083  
*B*, high power view of the tumor in *A*, showing rich vascularity and formation of capillary elements,  $\times 236$  Army Institute of Pathology, negative 102957

Dr Algernon B Reese, of New York, examined sections of the tumor and also voiced the opinion that the disease belonged to the von Hippel-Lindau group of lesions designated as angiomas of the retinae

The tumor was examined by Dr Frederick H Verhoeff, of Boston, whose comment follows "The cells resemble those of proliferating capillaries and appear to be derived from capillaries I think there is little neuroglia in the tumor proper, and I should not think otherwise unless a stain for neuroglia showed many neuroglia fibrils within the tumor Since the tumor is an angioma, it may belong to the von Hippel group, in spite of its unusual location However, I cannot make such a diagnosis without evidence other than the histologic character of this particular tumor It does not resemble the growth associated with tuberous sclerosis The blood is stained poorly, a fact which makes it difficult to perceive the true nature of the tumor I think the tumor is a hemangioendothelioma"

#### COMMENT

A case of von Hippel's angiomas of the retinae in an Army medical officer aged 40 is reported The tumor was situated immediately adjacent to the optic nerve head, leading to the preoperative impression of a malignant tumor of the optic nerve It is of further interest to note that a similar lesion has been seen in another military patient, as recently reported by Wilder<sup>3</sup>

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<sup>3</sup> Wilder, H C Intra-Ocular Tumors in Soldiers, World War II, Mil Surgeon 99 459 (Nov ) 1946

# SCLEROMALACIA PERFORANS

Report of a Case

MELVIN HARBATER, M D

MANHASSET, N Y

IN 1934 van der Hoeve<sup>1</sup> reported a new disease of the eye, which he called scleromalacia perforans. He concluded that the disease was a degenerative rather than an infectious process and that it usually accompanied rheumatoid arthritis. He accurately noted the early yellowish excrescences and the holes in the sclera which succeeded them, producing exposure of the uvea and the characteristic picture of the disease.

Occasional reports appeared after this, but they were so few that one must conclude that the disease is exceedingly rare. In 1938 Verhoeff and King<sup>2</sup> collected 14 cases from the literature, on the basis of an analysis of these cases, with 1 of their own, they gave the first pathologic report of the condition. In their summary, they stated, "Histologically, in their initial state the scleral nodules are essentially similar to the subcutaneous nodules of rheumatoid arthritis." Since 1938 1 case has been reported by Eggers<sup>3</sup> and a few cases have been mentioned by discussants of other cases. The present case is therefore reported in order that another instance of a rare disease may be added to the scanty literature and that attention may be called to an associated degeneration—marginal dystrophy of the cornea.

According to Verhoeff and King,<sup>2</sup> the lesion starts as a small elevated, yellowish nodule, which consists of a small, central, sterile abscess, surrounded by several layers of epithelioid cells. Fragments of necrotic sclera can be seen, and plasma cells and fibroblasts are present in the scleral clefts, beyond the wall of epithelioid cells. Where the process is severe, the plasma cells undergo colloid degeneration,

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Read at a meeting of the New York Academy of Medicine, Section of Ophthalmology, Oct 20, 1947

From the Ophthalmological Service of Queens General Hospital, W. Guernsey Frey, M D, Director

1 van der Hoeve, J Scleromalacia Perforans, Arch Ophth **11** 111 (Jan) 1934

2 Verhoeff, F H, and King, M J Scleromalacia Perforans, Arch Ophth **20** 1013 (Dec) 1938

3 Eggers, H Necroscleritis Nodosa Associated with Chronic Arthritis, Arch Ophth **23** 501 (March) 1940

and the underlying uvea degenerates. In a variable period, the contents of the abscess are extruded and an area of uvea is exposed. This area is usually covered by a thin layer of fibrous tissue. The conjunctiva may cover the defect, or only the borders of the defect. The pathologic changes are confined to the anterior portion of the sclera.

The disease characteristically occurs in the sixth, seventh and eighth decades of life. In the great majority of cases reported there was severe rheumatoid arthritis of long duration. The onset is usually insidious, with little or no pain and without visual disturbances. The scleral excrescence is accompanied with a localized area of scleral injection and superficially resembles episcleritis. In some cases the abscess is absorbed without sequestration of scleral tissue and no breakdown occurs. In such cases the diagnosis may not be made. In others, in a variable period (three to four weeks in this case) the nodule opens and discharges its content, leaving a small area of exposed uvea, which is the characteristic lesion. With the formation of similar foci about the original lesion, and their breakdown, the defects become coalescent, leaving large scleral holes.

A low grade iridocyclitis may complicate the disease at some stage of its progression. Both Eggers<sup>3</sup> and Kiehle<sup>4</sup> reported iritis in their cases. Van der Hoeve<sup>1</sup> reported atrophy of the iris in 1 of his cases and endophthalmitis in 1 of Rochat's cases. Eggers' case, which was of a fulminating character, ended with hemorrhages in the vitreous and sclerosing keratitis. Verhoeff and King<sup>2</sup> found no report of central corneal opacities in any case and noted mention of cataract in only 3 cases.

The disease may involve only one eye, or it may be bilateral. The duration is variable, and vision is not seriously affected by the scleral disease, but, as intraocular complications develop in most cases, the prognosis for vision is poor.

There is no known treatment of any value. Oast<sup>5</sup> reported a good result with ultraviolet irradiation in his case, but this patient did not have rheumatoid arthritis. Duke-Elder<sup>6</sup> mentioned placing a mucous membrane graft to cover the scleral hole. There is no report on the value of this procedure.

#### REPORT OF CASE

*History*.—On Jan 16, 1947, E. K., a white woman aged 70, was admitted to the Queens General Hospital for treatment of mild pneumonitis, which resolved in a few days. The patient had been bedridden for the past two years because of rheumatoid arthritis involving most of the joints of the body. When the patient was 30 years of age, the disease began in the right shoulder and had gradually involved

4 Kiehle, F. Scleromalacia, *Am J Ophth* **20** 265 (June) 1937.

5 Oast, S. P. Scleromalacia Perforans, *Arch Ophth* **17** 698 (April) 1937.

6 Duke-Elder, cited by Kiehle in discussion on Verhoeff and King.<sup>2</sup>

the knees, ankles, hands, wrists, elbows, hips and spine. She had received many types of therapy, including massive doses of vitamin D and gold salts, without appreciable benefit. About one year before her admission the patient began to have pain, burning and lacrimation of the eyes with gradual loss of vision.

*Ocular Examination*—The eyes were kept closed, although the patient could open them voluntarily, she could not keep them open for more than a few seconds. Vision was limited to light perception in the right eye and consisted in counting fingers at 2 feet (60 cm) in the left eye. Both corneas were clear, and the pupils were miotic and irregular. The pupils could not be dilated with atropine owing to the presence of dense posterior synechias. The lenses showed early cataractous changes, and the fundi could not be observed. Tension in each eye was very low, being below 10 mm (Schiotz). The lids were normal. The conjunctivas were diffusely reddened and thickened, and there was a scanty, dirty gray exudate in



Fig 1—Direct view of left eye, showing large scleral hole and exposed uvea above, with smaller hole below and developing area temporally

the lower fornices. There was profuse lacrimation during the examination. In each eye, 4 mm above the limbus, there were scleral holes, measuring 3 by 4 mm. In the right eye, on the nasal side of the limbus, there were two similar areas, measuring less than 1 mm in diameter. The uvea could be readily seen lying under a thin layer of transparent fibrous tissue. The conjunctiva overlapped these areas slightly. There were deep grooves in both upper limbal areas, with a steep shelf on the corneal side and a sloping shelf on the scleral side.

*Laboratory Studies*—Laboratory examinations did not reveal anything remarkable. The Wassermann reaction of the blood was negative. Chemical analysis of the blood showed urea nitrogen, 15 mg, albumin, 4.3 Gm, globulin, 2.1 Gm, cholesterol, 175 mg, cholesterol esters, 110 mg, and sugar, 125 mg per hundred cubic centimeters. The red cell count was 3,770,000, with 10 Gm of hemoglobin, and the white blood cell count was 10,900, with 90 per cent polymorphonuclear



leukocytes and 10 per cent lymphocytes. The urine was normal. Roentgenographic examination revealed partial demineralization of the entire skeleton. The joint spaces were narrowed, and their surfaces were eroded in the carpal, knee, hip and vertebral areas.

*Subsequent Course of Illness*—The patient was given local instillations of penicillin (1 cc, equivalent to 2,500 units) every two hours, atropine and hot compresses were also used. In a few days there was considerable subjective improvement, the discharge disappeared, and the conjunctiva became paler. However, there was no change in the general appearance of the eyes. The pupils failed to dilate, and two weeks after her admission a small yellow-gray excrescence was noted in the sclera of the right eye. Three weeks later this had disappeared, leaving a small hole. These holes seemed to enlarge by a gradual necrosis of the scleral tissue. Occasionally excrescences appeared, but the greatest progression of the lesion seemed to be due to a gradual melting away of the sclera at the margin of a defect. On April 3, endophthalmitis appeared in the right eye, the cornea grad-



Fig 2—Somewhat lateral view, showing deep superior temporal furrow in corneal limbus. The white areas are due to defects in the photograph.

ually clouded, and light perception was lost. Two weeks later, while attempting to photograph this eye, I saw the marginal furrow in the cornea perforate and the uvea bulge through the large scleral defect above the limbus. The eye became painful and was enucleated. At the time of this report, the left eye has suffered reduction in vision to perception of light, and scleral holes almost ring the cornea. The cornea is opacifying, and it is likely that the eye will become painful in time and will require enucleation.

*Pathologic Report* (Dr Alfred Angrist)—The specimen consisted of a globe, which was distorted and collapsed, with a large perforation at the limbus. The cornea presented an irregular epithelial cover, with partial loss of epithelium. The lens was absent. The iris was adherent to the cornea throughout. The retina and choroid had been detached in fixations. The sclera showed a large area of defect, with several similar smaller areas.

In microscopic section the cornea showed necrosis of the lamellas in the substantia propria. Here the collagenous fibers were swollen and appeared homogeneous, with basophilic detritus and granularity. Adjacent to such areas, considerable infiltration with polymorphonuclear leukocytes was present, with proliferating fibroblastic tissue. This was prominent in the region of the perforation, where Descemet's membrane was folded. The corneal epithelium had grown downward into the region of the perforation. Some proliferating nodules of large fibroblastic cells were seen beneath Descemet's membrane. The adjacent conjunctiva showed nonspecific inflammation and congestion.

The sclera showed zones of central necrosis with granular debris, suggesting disruption of inflammatory cells, these zones were surrounded by fibroblasts and epithelioid cells, which had a tendency to radial arrangement. In such areas an occasional giant cell was seen. One such cell had a characteristic Langhans arrangement of the nuclei. The necrotic areas in the sclera surrounded by zones of epithelioid and round cells were more extensive than are usually the subcutaneous nodules found in rheumatoid arthritis.

The uvea showed inflammatory infiltration, especially in the iris and the ciliary body, the infiltrate was much less conspicuous posteriorly. Numerous hemorrhages were present in the retina, choroid and ciliary body. The retina was considerably disorganized and folded, with extensive destruction of the neuroepithelium. There was a notable reduction in the number of ganglion cells.

#### SUMMARY

A case of scleromalacia perforans is described and added to the scanty literature of this disease. The clinical appearance of the lesion and the pathologic features conformed closely to the description by Verhoeff and King. The disease accompanied chronic rheumatoid arthritis of long standing and, in the course of about twenty months, slowly progressed to involve most of the anterior portion of the sclera in a necrotizing process. The eyes have become blind as a result of an accompanying uveitis. An unusual feature of this case was an associated marginal necrosis of the cornea.

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# CONGENITAL PTOSIS

## A Classification of Two Hundred Cases

RAYNOLD N. BERKE, M.D.

HACKENSACK, N. J.

THE PURPOSE of this paper is to present a classification of congenital ptosis illustrating its diverse and complicated nature. Such a presentation is desirable because the operative results of congenital ptosis, in the hands of experienced surgeons, depend on two conditions: (1) the nature of the ptosis present and (2) the type of operation selected. This study, therefore, is designed to simplify the classification of congenital ptosis and to assist the surgeon in selecting the proper procedure for each type of ptosis.

This classification of ptosis is based on a personal survey of the hospital records of 200 consecutive cases of ptosis seen at the Institute of Ophthalmology, Presbyterian Hospital of New York City, during the past fifteen years. The original preoperative observations were made by various members of the attending and resident staffs. In all cases the vision was recorded for each eye, when possible, the vertical widths, and sometimes the lengths, of the two fissures were measured, both with and without assistance of the frontalis muscle, the movements of the extraocular muscles were carefully examined, especially those of the superior rectus, the presence or absence of function of the levator palpebrae was noted in all cases, and the position of the upper lid fold in each eye was often also noted. The cocaine test, to determine the function of Muller's muscle in the upper lid, was rarely made because, in the few cases in which this test was done, it was of no practical value in indicating what operation should be performed. Moreover, tests for corneal sensitivity and measurements of the width of the upper tarsus were seldom made because most patients were children. Because of lack of cooperation in some cases, especially in young children, it was difficult or impossible to be certain that the function of the superior rectus was entirely normal on the side of the ptosis because the ptotic lid often could not be adequately elevated manually to expose the cornea. In other cases it was difficult to ascribe the limitation of motility to any group of muscles. Cases in which the superior oblique and the external rectus were the only fully active extraocular muscles were considered instances of congenital paralysis of the third nerve. In other cases some weakness of all

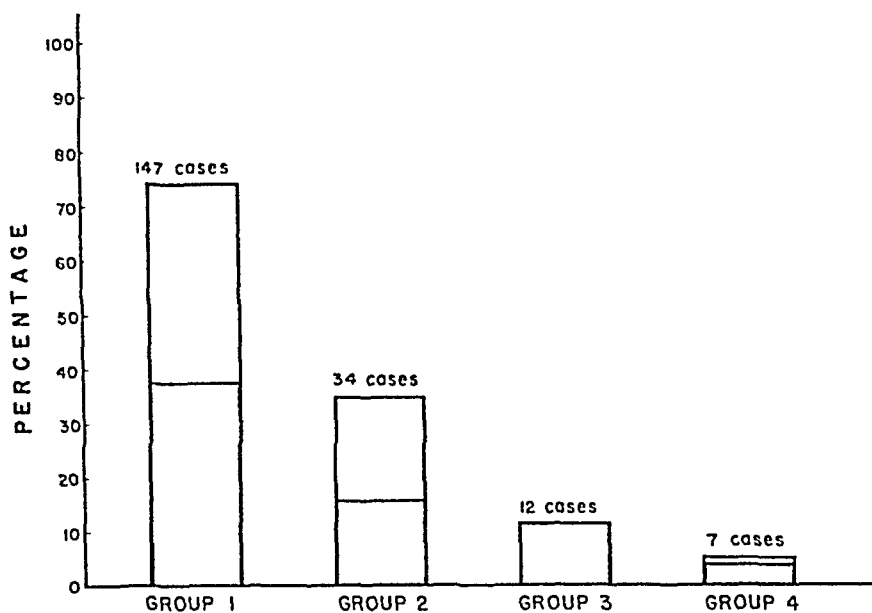
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From the Institute of Ophthalmology of Presbyterian Hospital of the City of New York

the extraocular muscles was present. Such a condition was considered due to congenital aplasia of all the extraocular muscles. In 1 of these cases operation revealed no elasticity of the inferior rectus muscle, presumably the result of congenital fibrosis. Cases of ptosis associated with Duane's retraction syndrome were not included in this series, for in this syndrome the ptosis is due to retraction of the globe and not to weakness of the levator muscle. No cases of acquired ptosis were included in this survey.

#### CLASSIFICATION OF PTOSIS

Ptosis may be classified in various ways, in accordance with the purpose the classification is designed to serve. The purpose of the



Classification of 200 cases of congenital ptosis

Group 1 includes patients with a normal superior rectus muscle, group 2, patients with a weak homolateral superior rectus muscle either alone or combined with a weak homolateral inferior oblique, group 3, patients with the jaw-winking phenomenon, and group 4, patients with blepharophimosis. The clear rectangles indicate patients without function of the levator palpebrae, and the black rectangles, patients with normal function of the levator muscle.

present classification is to assist the surgeon in selecting the proper operation for each type of congenital ptosis. Careful examination of a number of patients will show that any case of congenital ptosis may be placed in one of four groups (chart). group 1, ptosis with normal function of the superior rectus muscle, group 2, ptosis with weakness of elevation due either to weakness of the superior rectus muscle alone or to weakness of the superior rectus and the inferior oblique muscles combined, group 3, ptosis associated with the jaw-winking phenomenon of Marcus Gunn, and group 4, ptosis associated with blepharophimosis (chart).

Group 1 was made up of 147 cases of congenital ptosis in which no weakness of the superior rectus or the inferior oblique muscle was noted. Therefore, in about 73.5 per cent of the entire series of cases of congenital ptosis ocular elevation was normal. Of the 147 cases, 105 were of unilateral and 42 of bilateral ptosis. Among the 105 cases of unilateral ptosis there were 1 case of exotropia, 5 cases of esotropia, 3 cases of overaction of the homolateral inferior oblique, 1 case of weakness of the homolateral inferior rectus and 1 case of overaction of each superior oblique muscle. Of the 42 cases of bilateral ptosis with normal elevation of the extraocular muscles, there were 2 cases of exotropia and 1 case of esotropia. Of the 147 cases in group 1, a complicating anomaly of the horizontal or vertical extraocular muscles was present in only 14 cases, or about 10 per cent.

Group 2 comprised 34 cases (or 17 per cent of the 200 cases) of ptosis associated with weakness of one or both of the homolateral extraocular elevator muscles. Of the 34 cases, weakness of the superior rectus alone was a complication in 10, being unilateral in 8 cases and bilateral in 2 cases. Of the 8 cases of unilateral ptosis with weakness of the homolateral superior rectus muscle, there were 3 of exotropia and 1 of esotropia. Of the 2 cases of bilateral ptosis with weakness of the superior rectus alone, 1 was of esotropia.

In about 12 per cent (24 cases) of the 200 cases there was a combined weakness of both the superior rectus and the inferior oblique muscle on the side of ptosis. Of the 24 cases 19 were of the unilateral and 5 of the bilateral form. The cases of unilateral involvement included 1 of exotropia, 1 of esotropia, 1 of proved fibrosis of the inferior rectus, 3 of what was thought to be a congenital paralysis of the third cranial nerve and 1 of weakness of all the extraocular muscles. Of the 5 cases of bilateral ptosis associated with bilateral weakness of the superior rectus and the inferior oblique muscles, paralysis of the third nerve was a further complication in 1 and weakness of all the extraocular muscles in 2.

It should be noted that in about 50 per cent (15 of 34) of the cases in group 2 the ptosis was complicated by some anomaly of the extraocular muscles besides the weakness of the superior rectus and/or the inferior oblique. In group 1, this complication was present in only about 10 per cent of the cases. This observation tends to show that if the vertically acting extraocular muscles are affected in ptosis, the horizontally acting muscles are more likely to be affected also, thus complicating the surgical correction.

Group 3 consisted of 12 cases of the jaw-winking (Marcus Gunn) phenomenon and comprised 6 per cent of the entire series of 200 cases. In all these cases the ptosis was unilateral, no cases of the

bilateral jaw-winking syndrome having ever been observed. In 5 of the 12 cases, the ptosis was uncomplicated by weakness of the superior rectus or the inferior oblique muscle, in 4 cases the superior rectus alone was weak (in 1 of which there was a further complication of exotropia), and in 3 cases there was combined weakness of the superior rectus and the superior oblique muscle. In 1 of these 3 cases a proved fibrosis of the inferior rectus produced the clinical picture of weakness of elevation. It is interesting to note that in 7 (58 per cent) of the 12 cases of the Marcus Gunn phenomenon a complicating anomaly of the extraocular muscles was present.

Group 4 consisted of 7 cases of ptosis associated with blepharophimosis, comprising 3.5 per cent of the entire series of 200 cases. In such cases there are short palpebral fissures, an abnormally wide distance between the inner canthi over the bridge of the nose and abnormally formed, S-shaped lids. In 1 of these 7 cases overaction of each superior oblique was present.

Of the 200 cases, the ptosis was unilateral in 145 (72.5 per cent) and bilateral in 55 (27.5 per cent). Of the 200 cases 147 (73.5 per cent) were instances of simple ptosis, while in 53 (26.5 per cent) the ptosis was complicated by imbalances of the vertically or horizontally acting extraocular muscles, these imbalances were represented by 7 cases of exotropia, 10 cases of esotropia, 41 cases of assorted vertical imbalances, 4 cases of congenital paralysis of the third nerve and 2 cases in which all the extraocular muscles were weak.

These figures demonstrate that ptosis is often a complicated condition in which other abnormalities of the extraocular muscles requiring surgical correction may be present. Proper treatment requires that these additional factors be carefully considered along with the ptosis, in order that satisfactory results may be attained.

Of these 200 cases, resection of the levator muscle was performed in 107 (53.5 per cent), and some modification of the Parinaud-Motais operation for correction of the ptosis, in 93 (46.5 per cent). Of the 107 cases in which the levator palpebrae was resected, the superior rectus muscle was normal in 76 (bilaterally in 21) (group 1), there was weakness of the superior rectus alone or combined with weakness of the inferior oblique in 23 (bilateral in 5) (group 2),<sup>1</sup> the jaw-winking phenomenon in 4 (group 3) and blepharophimosis in 4 cases (group 4). Of the 93 cases in which the Parinaud-Motais operation

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1 In some of these 23 cases there may have been little or no action of the levator, but the chances of success seemed better for correction of the ptosis by resection of the levator than by suspension of the upper lid from the already weak superior rectus. Therefore, resection of the levator palpebrae in this group may have been done in some cases showing little or no action of the muscle clinically.

was performed, there were a normal superior rectus muscle in 71 (bilateral in 20) (group 1), weakness of the superior rectus alone or combined with weakness of the inferior oblique in 11 (bilateral in 1) (group 2),<sup>2</sup> the Marcus Gunn phenomenon in 8 cases (group 3) and blepharophimosis in 3 (group 4)<sup>3</sup>

## COMMENT

Reports in the literature on the classification of ptosis are rare, the only comprehensive one being that of Spaeth,<sup>4</sup> who divided ptosis into 9 classes (page 357), and again into seven groups (page 364). He included in his classification acquired ptosis and ptosis associated with

*Eighty-Eight Cases of Congenital Ptosis Reported by Spaeth Compared with 200 Similar Cases from the Institute of Ophthalmology*

Group	Spaeth (88 Cases), Percentage	Berke (200 Cases), Percentage
1 Ptosis with normal superior rectus		
Unilateral	45.4	52.5
Bilateral	7.9	21.0
2 Ptosis with weakness of elevation		
Due to weakness of superior rectus alone		
Unilateral	29.9*	4.0
Bilateral	4.5	1.0
Due to combined weakness of superior rectus and inferior oblique		
Unilateral	5.6†	9.5
Bilateral	4.5†	2.5
3 Ptosis with jaw winking	2.2‡	6.0
4 Ptosis with blepharophimosis	§	3.5
	100 (88 cases)	100 (200 cases)

\* This percentage includes 5 cases of weakness of both superior rectus muscles with unilateral ptosis

† Spaeth classified these cases as paresis of the third and fourth nerves

‡ Spaeth mentioned the jaw winking phenomenon in his classification but did not cite the number or percentage of cases seen, but, judging from the rest of his figures cited, it must be about 2 per cent

§ Spaeth did not classify blepharophimosis by itself

Duane's retraction syndrome, types of ptosis which I have purposely omitted. Therefore, his percentages cannot be fairly compared with those given here. However, after 10 cases of acquired ptosis and 2 cases of Duane's retraction syndrome are eliminated from his series of 100 cases, 88 cases of congenital ptosis are available for statistical comparison with the 200 cases reported here. In the accompanying table, it will be noted that Spaeth did not find as many cases of

2 The Parinaud-Motais type of operation was usually not done when the superior rectus was weak except in cases in which the levator palpebrae was so weak as to result in failure, or in other cases in which a resection of the levator had already been done, with inadequate correction

3 The results of some of these 200 operations will be reported later. Berke, R. N. Motais Parinaud Operation for Ptosis. Report of Thirty-Five Cases, Arch Ophth (to be published)

4 Spaeth, E. B. Principles and Practice of Ophthalmic Surgery, Philadelphia, Lea & Febiger, 1944

ptosis with normal superior rectus muscles as I did (group 1), the superior rectus muscles being normal in 53 per cent of his cases and weak in 44.5 per cent (group 2), as compared with 73.5 and 17 per cent respectively, for the present series of 200 cases. This apparent discrepancy may be accounted for by the difficulty one experiences in cases of slight weakness of the superior rectus in being certain in the presence of ptosis whether the superior rectus muscle is fully active especially in young children, and by the fact that what one observer considers normal function, another will call slight or definite weakness. Moreover, some allowances must be made for the fact that the data in Spaeth's series were based on his own observations, whereas the clinical findings in the 200 cases reported here are the combined observations of several clinicians. The apparent discrepancy between Spaeth's findings and those reported here as to the bilaterality of ptosis (Spaeth found that in 7.9 per cent of the cases with a normal superior rectus the ptosis was bilateral, whereas the corresponding figure in my series was 21.0 per cent) may be due to the fact that it is sometimes difficult to be sure that both upper eyelids are not ptotic, especially when the ptosis is greater on one side. In such cases, in which the palpebral fissure on one side measures 7 mm, so that the upper lid uncovers the pupil, while that of the opposite side measures only 2 or 3 mm and the lid completely covers the pupil, some surgeons would consider the ptosis bilateral and unequal and other observers would consider the ptosis unilateral. Until some universal standard is accepted for measuring ptosis, differences such as those under discussion will occur.

#### TREATMENT OF PTOSIS

The criteria for a perfect operation for ptosis have previously been listed<sup>5</sup> but may be recited here:

- 1 The curve of the margin of the upper lid should overlap the cornea equally on the two sides, covering the upper part of the cornea when the lids are normally open.
- 2 The margin of the lid should be a smooth curve and similar in the two eyes, with no tendency to form a notch or Gothic arch, or to invert the lashes when the lids are wide open.
- 3 The superior palpebral crease should correspond on the two sides.
- 4 The eye should be capable of being widely opened and of being completely closed, both in forceful closure and in sleep.
- 5 Normal winking should be preserved.

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<sup>5</sup> Berke, R. N. Blepharoptosis, *Arch. Ophth.* **34**: 434-450 (Nov.-Dec.) 1945.



6 The vertical distance between the eyebrow and the margin of the upper lid should normally be the same in the two eyes

7 The upper lid of each eye should move synchronously with the globe in all directions of gaze

8 Diplopia or disturbing heterophoria should be absent

In a consideration of the surgical treatment of ptosis, it is interesting to note that over thirty years ago Beard<sup>6</sup> stated "All who have had much experience in this branch of ophthalmic surgery will agree that the results of ptosis operations, taken all in all, are far from brilliant" The same thing could be said today, in spite of the more than eighty surgical procedures proposed for the treatment of ptosis, and I believe it will have to be accepted that the surgical treatment of ptosis is still in many respects one of the unsolved problems of ophthalmology In my opinion there are three main reasons for this (1) the inherent nature of ptosis, (2) selection of the wrong type of operation and (3) use of the wrong technic in doing the operation selected Each of these factors plays an important part in the cosmetic and functional result, but I believe that the nature of the ptosis is the most important single factor in determining that result

There is no better way to obtain an over-all picture of the inherent and diverse nature of congenital ptosis than to study and analyze statistically a large number of cases The present study of 200 consecutive cases showed that all cases of congenital ptosis can be placed in one of four groups group 1, cases with a normal homolateral superior rectus muscle only, group 2, cases with a weak superior rectus muscle, group 3, cases of ptosis with the jaw-winking phenomenon of Marcus Gunn, and group 4, cases of ptosis with blepharophimosis The four groups were further subdivided into cases with and cases without function of the levator palpebrae (chart)

This classification is useful in the surgical treatment of ptosis because it indicates immediately what operation is most likely to be successful in correction of the ptosis In group 1, for example, there were 147 cases, comprising 73.5 per cent of the entire series, in which the superior rectus muscle was normal Of this number, 76, or 51.7 per cent had some function of the levator muscle, and 71, or 48.3 per cent, had no such function Because resection of the levator is the operation of choice in all cases of ptosis in which this muscle is active, it was indicated in 51 per cent of the cases in group 1 Because the superior rectus was normal in the rest of the cases, some modification of the Parinaud-Motais operation could be carried out in them All the cases in group 1, therefore, were instances of uncomplicated or simple

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6 Beard, W. H. *Ophthalmic Surgery*, Philadelphia, P. Blakiston's Son & Co., 1914, pp. 230-252

ptosis, in which there existed no problem as to the type of operation indicated. If the levator muscle was active, it should be resected, if not, the superior rectus should be utilized to correct the ptosis. Whichever operation is done in such cases, the results should be uniformly good, and failure, when it occurs, must be attributed to selection of the wrong type of operation or to faulty technic in the performance of the operation selected. For example, resection of the levator is likely to fail if the levator is completely paralyzed or absent. Moreover, both operations will result in failure if incorrectly performed.

In group 2, there were 34 cases of congenital ptosis with weakness of the homolateral superior rectus alone or combined with weakness of the inferior oblique. Of this number, function of the levator was present in 23, or 63 per cent, and resection of the levator was the operation of choice in these cases. The 11 cases without function of the levator were problem cases because resection of the levator could not be done with reasonable hope of success, nor could the weak superior rectus be utilized for lifting the lid. In such cases, in which both the superior rectus and the levator are paralyzed, some surgeons utilize the lifting power of the frontalis muscle to support the lid.

Even cases with action of the levator muscle in group 2 were problem cases in some respects, because in several instances the hypotropia associated with ptosis required one or more operations to correct it. White<sup>7</sup> called this condition pseudoptosis because when the ptotic eye is used for fixation, the eyelid and the eyeball assume a more or less normal aspect in the primary position, while the upper lid and the cornea of the fellow eye shoot far up. White expressed the belief that in these cases the hypotropia should be corrected before correction of the ptosis is attempted. Wheeler<sup>8</sup> agreed with this thesis and resected the homolateral superior rectus and inferior oblique muscles when both muscles were weak, before performing one of the types of the Parinaud-Motais operation. Kirby<sup>9</sup> decided, however, after several unhappy results with this program, that it might have been better in some of his cases to suspend the lid from the frontalis muscle after correcting the hypotropia than to utilize the already weak superior rectus for this purpose.

Whatever is done for patients with ptosis and hypotropia requires several operations, and the results are nearly always disappointing.

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7 White, J. W. (a) The Choice of the Fixing Eye in Paralytic and Non-Paralytic Strabismus, *Tr Am Ophth Soc* **41** 319-324, 1943, (b) Paralysis of the Superior Rectus and the Inferior Oblique Muscle of the Same Eye, *Arch Ophth* **27** 366-371 (Feb) 1942.

8 Wheeler, J. M. Personal communication to the author.

9 Kirby, D. K. Paralysis of Ocular Elevation With and Without Ptosis, *Tr Am Ophth Soc* **43** 218-239 1945.

Failure, therefore, must be attributed to the nature of the ptosis and not to selection of the wrong operation or to faulty technic. Certainly, the surgeon cannot be expected to create a normally functioning upper lid and eyeball when some normal muscle tissue does not already exist.

In group 3 were 12 cases of the jaw-winking phenomenon of Marcus Gunn. In most of these cases the ptosis completely disappeared when the lower jaw was depressed or when it moved to the opposite side. With the jaw in this position, the upper lid often overshot the mark, especially when the subject was looking down, so that the sclera above the upper limbus was exposed. Even though the levator muscle was active, resection of this muscle was contraindicated because shortening of the levator muscle would only enhance the jaw-winking phenomenon. The most logical approach to the problem is that suggested by Dunnington,<sup>10</sup> Carroll<sup>11</sup> and Spaeth,<sup>12</sup> in which the jaw-winking phenomenon is cured by first performing a complete tenectomy on the levator muscle, thus abolishing the jaw-winking act and simultaneously converting what is usually partial ptosis to a complete one, and then, at the same time, correcting the ptosis thus produced by utilizing the lifting power of the superior rectus or the frontalis muscle. Unfortunately, the superior rectus is not always normal in these cases, the homolateral superior rectus muscle being weak in 5 of the 12 cases of the series and a weak superior rectus being combined with a weak inferior oblique muscle in 3 additional cases. Spaeth<sup>12</sup> stated the belief that in all cases of the jaw-winking phenomenon the lid should be suspended from the brow after the levator muscle is tenectomized. In these cases, the jaw-winking phenomenon and the ptosis can be corrected, but usually at the expense of producing some other deformity. If the frontalis muscle is used to support the upper lid, the forehead must be wrinkled and the brow elevated to raise the lid. If the superior rectus is utilized, the lagophthalmos and hypotropia develop. Thus, one is forced to correct one deformity by producing another, less conspicuous, one. This must be so because of the nature of the ptosis.

Group 4 comprised 7 cases of ptosis associated with blepharophimosis. In some of these cases there were in addition to the ptosis and the blepharophimosis, abnormal development of inner canthi. These cases are problem cases and require special consideration. Before the ptosis is corrected, the phimosis must be cured by lengthening the palpebral fissure. This can be partially accomplished by an external canthoplasty combined with an operation to shorten the distance between

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10 Dunnington, J. H. Personal communication to the author.

11 Carroll, F. C. Personal communication to the author.

12 Spaeth, E. B. The Marcus Gunn Phenomenon. Discussion, Presentation of Four Instances and Consideration of Its Surgical Correction, *Am J Ophth* 30: 143-158, 1947.

the inner canthus. After the fissures have been lengthened, the ptosis should be corrected by resection of the levator if this muscle is active or, if the levator is paralyzed, by utilization of the lifting power of the superior rectus or the frontalis muscles.

Cases of this sort present one of the most difficult problems in correction, and whatever functional or cosmetic improvement the surgeon can achieve must be considered an accomplishment. Since the surgeon is not supplied with adequate structures to work on, his failure to correct the defects satisfactorily must be attributed to the nature of the ptosis, and not to faulty judgment or technic.

#### SUMMARY AND CONCLUSIONS

A statistical study has been made of 200 consecutive cases of congenital ptosis seen at the Institute of Ophthalmology during the past fifteen years. Of the 200 cases, there were normal superior rectus muscles in 147 (73.5 per cent), weakness of the homolateral superior rectus alone or combined with weakness of the homolateral inferior oblique in 34 (17 per cent), the jaw-winking phenomenon of Marcus Gunn in 12 (6 per cent) and ptosis associated with blepharophimosis in 7 (3.5 per cent). Of the 200 cases, the ptosis was unilateral in 145 (72.5 per cent) and bilateral in 55 (27.5 per cent), simple in 147 (73.5 per cent) and complicated by horizontal or vertical anomalies in 53 (26.5 per cent). In 107 (53.5 per cent) of the 200 cases, sufficient action of the levator muscle existed to justify resection of the muscle as the operation of choice, while in 93 cases (46.5 per cent) there was no such function and the patients were candidates for some modification of the Mouton-Parinaud operation or for the frontalis type of procedure.

This classification of congenital ptosis is useful in that it gives an over-all picture of the complicated nature of ptosis and, at the same time, is helpful to the surgeon in selecting the proper surgical procedure. It also gives him some idea of what to expect cosmetically and functionally from operations for the various types of congenital ptosis.

In the hands of experienced surgeons inadequate cosmetic and functional correction of ptosis depends on the inherent complicated nature of the ptosis rather than on faulty judgment or technic. Therefore, one should not expect perfection in every case of ptosis because the cosmetic and functional result in each case must be judged on the nature of the ptosis present.

# Ophthalmologic Reviews

## INTRAORBITAL TUMORS

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A CORRELATION of the clinical data with the histologic features is especially important in the case of intraorbital tumors, for, to a greater extent than in most ophthalmic diseases, the treatment and prognosis are determined by the results of microscopic examination. Accordingly, it is the purpose of this report to summarize the data relating to the pathology, semeiology and history of the disease in a series of 222 cases of tumors, selected wholly on the basis of their situation in the orbit, from the collection in the Registry of Ophthalmic Pathology, of the Army Institute of Pathology. Since the material was available only as gross and microscopic preparations, emphasis will necessarily be on the pathology, in this way, this study differs from those of Birch-Hirschfeld<sup>1</sup> and Reese<sup>1a</sup>.

The structure and development of the orbital contents suggest the possibility of a wide variety of tumors. The incidence of each type in this series is indicated in the accompanying table.

### PRIMARY TUMORS

In this series, 184 tumors, both benign and malignant, were primary in the orbit, and only 38 were secondary. The primary tumors have been classified according to their origin and will be discussed in the order of this grouping.

### MESENCHYMAL TUMORS

*Connective Tissue Tumors*—The connective tissue tumors in this series numbered 43. In 30 cases the tumors were benign, and, of these, the lipoma was the commonest variety, being present in 19 cases. Lipomas were usually situated anteriorly in the orbit, and, except in 2 cases, in which the tumor was in a posterior location, the presenting symptom was that of a mass. Ptosis in 2 cases indicated that the lid

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From the Registry of Ophthalmic Pathology, Army Institute of Pathology, Washington, D C.

Read before the Section on Ophthalmology of the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

1 Birch-Hirschfeld, A, in Graefe, T, and Saemisch, T. *Handbuch der gesamten Augenheilkunde*, Berlin, Julius Springer, 1930, vol 1, pt 1.

1a Reese, A B. *Orbital Tumors and Their Surgical Treatment*, Am J Ophth 24 386-394 (April), 497-502 (May) 1941.

was also involved. In the 2 cases of posterior tumor the lipoma was discovered when the eye was enucleated because of exposure keratitis. In another case enucleation was performed because of a macular mass in a blind eye, and a large lipoma was noted surrounding the optic nerve (fig 1A).

*Intraorbital Tumors*

<b>Primary Tumors</b>	
I Mesenchymal origin	
A Connective tissue	
Benign	
Lipoma	19
Osteoma	5
Lipolipoma	2
Lipoma	2
Chondroma	1
Rhabdomyoma	1
Malignant	
Undifferentiated sarcoma	7
Rhabdomyosarcoma	4
Liposarcoma	2
B Vascular system	
Benign	
Hemangioma	24
Malignant	
Angiosarcoma	1
C Hematopoietic system	
Lymphoma, lymphosarcoma	22
Hodgkin's disease	2
Plasmocytoma	1
II Epithelial origin	
Mixed tumor	25
III Neural and meningeal origin	
Benign	
Neurofibroma	17
Meningioma	17
Glioma	5
Malignant	
Neurofibrosarcoma	9
IV Developmental fault	
Dermoid	17
Teratoma	1
Total	184
<b>Secondary Tumors</b>	
Carcinoma	24
Neuroblastoma	6
Melanoma	6
Pituitary adenoma	1
Retinoblastoma	1
Total	38
Total series of tumors	222

The tumor was bilateral in 2 cases, both the patients being over 58 years of age. There was no other noteworthy feature in the age or sex distribution. The tumor had been noticed since birth in 4 patients, the oldest of whom was 23 years of age. In all but 2 cases the lipoma was treated by simple excision of the mass, the globe, as well as the mass, was removed in 2 cases.

Pathologically, the lipomas were composed of lobules of adult fat. A capsule was not apparent histologically, hence the tumors were indistinguishable from normal orbital fat, and the diagnosis of tumor



Fig 1—Lipoma (A) Gross photograph, showing posterior position of tumor A I P neg no 181038, (B) photomicrograph, showing tumor surrounding optic nerve and mass of organized submacular hemorrhage  $\times 10$ , A I P neg no 101099

was based on the surgeon's statement. The microscopic appearance of the tumor which surrounded the optic nerve is shown in figure 1 B. In 1 instance macrophages invading the mass represented a reaction to degenerating lipid.

Classified as osteoma was an abnormal bony proliferation in the orbit in 5 cases (fig 2*A*). In 1 case the lesion was associated with a dermoid and in a second with a meningioma. In 3 instances the masses were autonomous tumors, in the roentgenogram 2 of these appeared to compromise the frontal sinus.

Two tumors, containing a considerable quantity of fibrous tissue as part of the neoplastic process in addition to the fat cells, were regarded as fibrolipomas.

Two benign tumors of connective tissue origin which were entirely fibrous in nature were classified as fibromas. One of these was situated anteriorly and was composed of dense collagenous tissue. It was attached to, and probably arose in the tendon of an extraocular muscle. The second fibroma, the presence of which was suspected because of increasingly choked disk, was somewhat more cellular and edematous and was observed to have arisen in the dual sheath of the optic nerve (fig 2*B*).

One tumor of cartilaginous nature, a chondroma, was attached to the superior orbital margin.

A tumor warranting more detailed comment because of its rarity was a rhabdomyoma which had occurred in the orbit of an 18 year old Negro. The presenting complaint was exophthalmos which had increased 8 mm in seven years. At operation it was noted that the tumor was attached to the superior rectus muscle and filled the upper portion of the orbit. It measured 30 by 17 by 12 mm. Microscopically, the neoplasm consisted of abnormal striated muscle cells (fig 2*C*), the fibers of which were irregularly disposed and hence sectioned in random planes, in contrast to the regular arrangement of the strands in normal rectus muscle. In view of the absence of evidence of inflammation, recent or old, and the disparity between the size of the lesion and that of normal muscle, this mass was considered neoplastic, and not degenerative or inflammatory. Because of the maturity of the cells it was presumed to be benign.

In addition to the 30 benign tumors described, there were 13 malignant tumors of connective tissue origin. In contrast to the generally anterior situation of the benign tumors, the malignant tumors were noted posteriorly in the orbit. Exophthalmos was the prominent symptom in 11 cases, and in 1 case there was associated ptosis, apparently of sudden onset. All but 3 of the patients were less than 20 years of age, and one-half were less than 12 years of age.

Seven orbital tumors were classified as undifferentiated sarcomas. Pleomorphism and hyperchromatism of cells in stroma having connective tissue features characterized these tumors, mitotic figures were not uncommon, and occasional giant and other bizarre forms were present. Occasional vacuoles within the cells took a stain for fat, but



the presence of fat is common in rapidly growing sarcomas, often as a degenerative product, and does not alone indicate an origin in lipid tissue or a differentiation toward mature fat cells. Three of the 7 patients with an undifferentiated sarcoma died in from three to twenty-four months after operation, 2 were alive with recurrence after

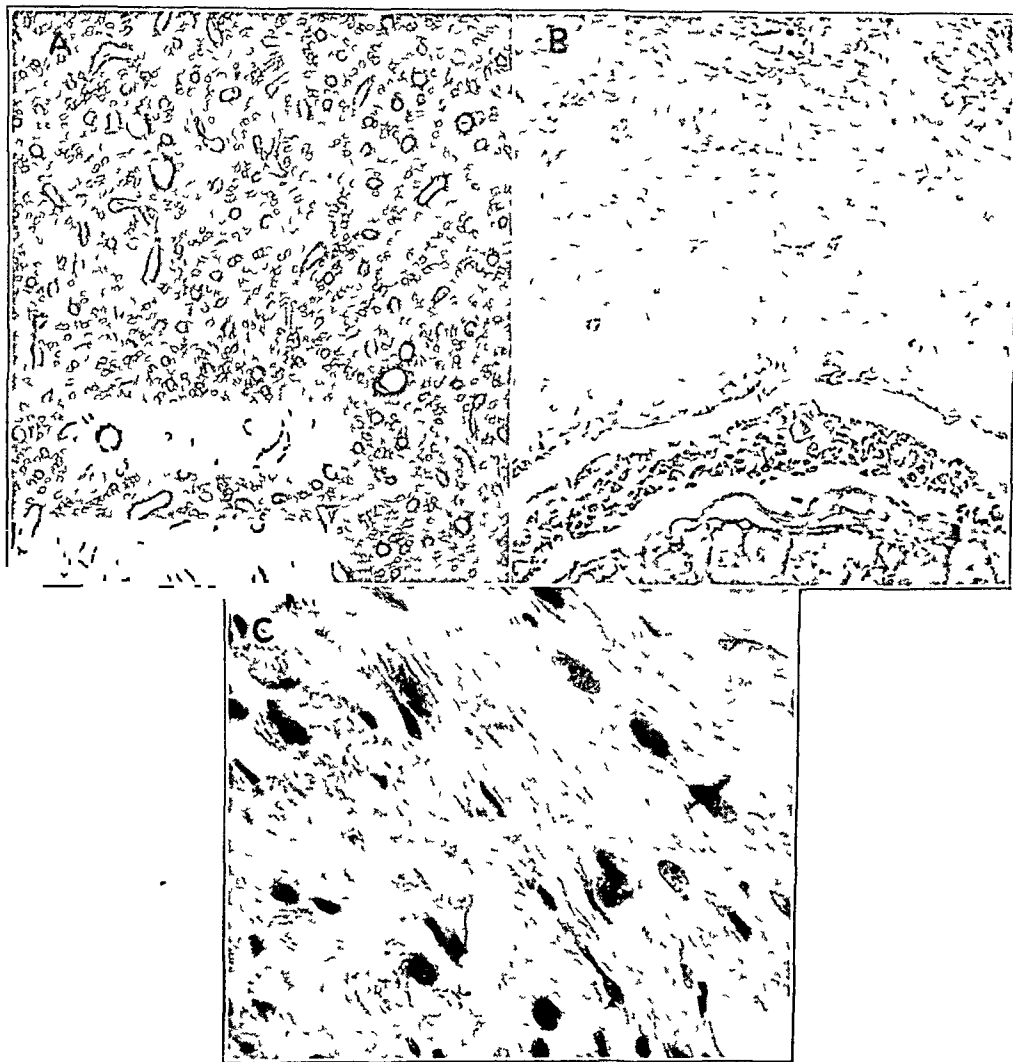


Fig 2—(A) Osteoma,  $\times 40$ , A I P neg no 104581, (B) dural fibroma,  $\times 40$ , A I P 101098, (C) rhabdomyoma,  $\times 300$ , A I P neg no 101097

eight and eighteen months, respectively, and 1 was alive and well five years after operation. The status of 1 patient was unknown.

Four of the 13 malignant tumors included in the connective tissue series were regarded as rhabdomyosarcoma, since they appeared to have arisen in striated muscle. All the patients having this tumor were less than 10 years of age. Histologically, the tumors were characterized by cross striations in the cytoplasm, which was eosinophilic, often

abundant and occasionally terminating in ribbon-like ends. The nuclei were often large, occasionally of giant size, rarely multiple (fig 3)

Two patients with rhabdomyosarcoma died within a year, and the other 2 were alive ten and fourteen years after operation. The clinical impression of the presence of a capsule in the specimen from a patient who died was apparently of little prognostic value. It is probable that the structure was a pseudocapsule, resulting from compression of the surrounding tissue. In this instance the first recurrence was noted within four months, and a few months after the second excision the

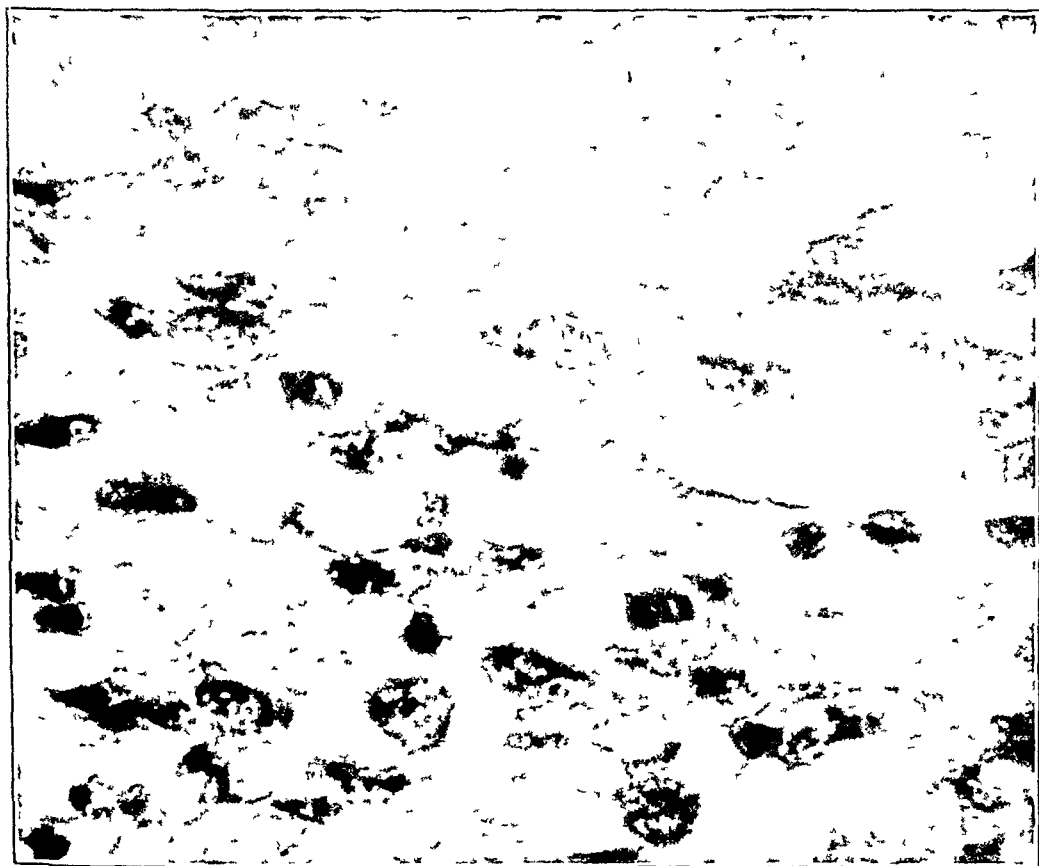


Fig 3—Rhabdomyosarcoma, showing anaplasia and cross striations,  $\times 450$ , AIP neg no 101203

orbit was filled with a mass, which continued to grow until it was more than 4 inches (10 cm) in diameter. Autopsy revealed widespread metastases.

Two other malignant tumors of connective tissue, fibrosarcomas, were composed of collagen-producing cells. One of the patients was well three and one-half years after operation, and the other had noted recurrence ten months after operation.

In summary, the benign connective tissue tumors were characteristically of random age distribution and were situated anteriorly in the orbit, and the majority were lipomatous. In contrast, the malignant

tumors occurred in young patients and, arising posteriorly in the orbit, caused exophthalmos. The cellular immaturity of the malignant tumors often precluded classification of cell types. The median duration of symptoms related to benign tumors was three years, whereas one-half the malignant tumors had produced symptoms less than two months before the patient consulted the surgeon. Approximately one third of the patients with malignant tumors died early in the course of the disease, one-third are living but are known to have recurrence and one-third are known to be living and well at least five years after removal of the tumor. In view of the poor results of therapy, which was conservative in the majority of cases in this series, it would seem that if the diagnosis of sarcoma is confirmed microscopically, early exenteration of the orbit might better the prognosis.

*Tumors of Vascular Origin*—The 25 neoplasms of the vascular system comprised almost 15 per cent of the primary orbital tumors. Eleven of these were noted in patients under 3 years of age. Many of the vascular tumors were probably congenital, although the initial symptoms often became evident after birth, and in 1 patient as late as at 60 years of age. One-half the lesions were situated anteriorly in the orbit, and one-half caused exophthalmos. Information was not available as to whether there were coexistent angiomas of the skin.

Histologically, these tumors were disposed in a continuum from a structure which contained well developed cavernous channels (cavernous hemangioma), through neoplasms with smaller vessels (capillary hemangioma) to those characterized by high cellularity and small, inconstant blood channels (hemangioendothelioma, hemangioblastoma or, in the most malignant form, angiosarcoma).

Sixteen tumors in this group were of the cavernous variety, in which connective tissue trabeculae of varying thickness separated endothelium-lined vascular channels of inconstant size, containing blood (fig 4A). In 2 specimens, all of the spaces were relatively small, of the order of capillaries (fig 4B). In 1 of these, additional connective tissue trabeculae divided the tumor into lobules, in the other, the tumor was situated within the substance of the lacrimal gland. In 3 tumors there was moderate diffuse fibrosis between the endothelial cells, among which were small vascular channels. This presumably regressive change produces the "sclerosing hemangioma." In 3 of the remaining specimens, small vascular channels, in which it was often difficult to discern erythrocytes, traversed the sheets of endothelial cells. These cells were composed of scanty cytoplasm and oval vesicular nuclei, in which occasional nucleoli were noted. These densely cellular tumors, which are, however, cytologically quiescent and carry no implication of malignancy, represent the benign hemangioendothelioma, or juvenile hemangioma (fig 4C).

This classification is based on the predominant histologic appearance. In some specimens, however, features of more than one type were present, dependent perhaps on the age or differentiation of the tumor. The specimen which best illustrates this phenomenon is one

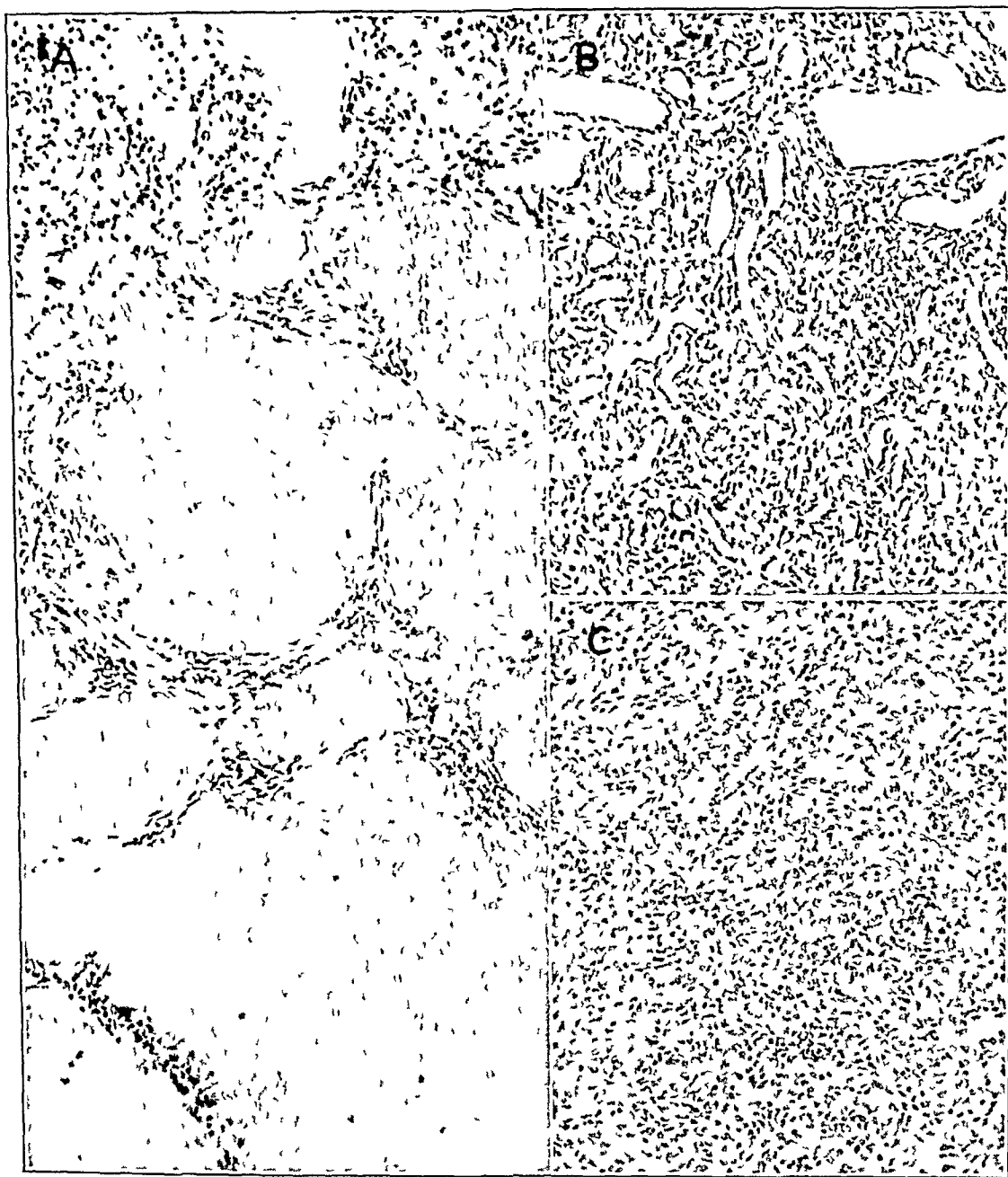


Fig 4—(A) Cavernous hemangioma,  $\times 114$ , AIP neg no 104514, (B) capillary hemangioma,  $\times 135$ , AIP neg no 100702, (C) hemangioendothelioma, benign (juvenile hemangioma),  $\times 160$ , AIP neg no 100701

in which evidence of cytologic activity, including numerous mitotic figures, suggests malignant potentialities of the tumor, an angiosarcoma, although there is no follow-up information in this recently registered case. Figure 5, of low magnification, includes a perforated corneal

ulcer and a massive tumor made up of both cavernous and densely cellular areas. The cavernous areas, in which some of the spaces contained a protein material similar to that seen in the lymphangioma, are shown under higher magnification in figure 6A. In other fields, smaller channels and highly cellular areas were noted, and within the sheets of endothelial cells clusters were present which simulated the capillary buds seen in granulation tissue (fig 6B). Since the potentiality of a tumor is determined by its most active element, tumors such as the one just described were classified as hemangioendotheliomas. The invasive tendency of this type of tumor is illustrated by the



Fig 5—Hemangioendothelioma, malignant (angiosarcoma),  $\times 2$ , A I P neg no 102435

extension of a portion of the tumor into the bony orbital wall (fig 6C) and by invasion of voluntary muscle (fig 7).

Tumors of the vascular system are rarely malignant, and a metastasizing angioma was not included in this series. More frequently, because of the technical difficulty of orbital surgery, there remains a modicum of tumor, especially of the highly cellular forms, leading to clinical recurrence. The scanty follow-up data were of no assistance in confirming these generally accepted principles.

*Tumors of Hematopoietic System*—There were 25 tumors derived from the blood-forming tissues, excluding, of course, the many masses

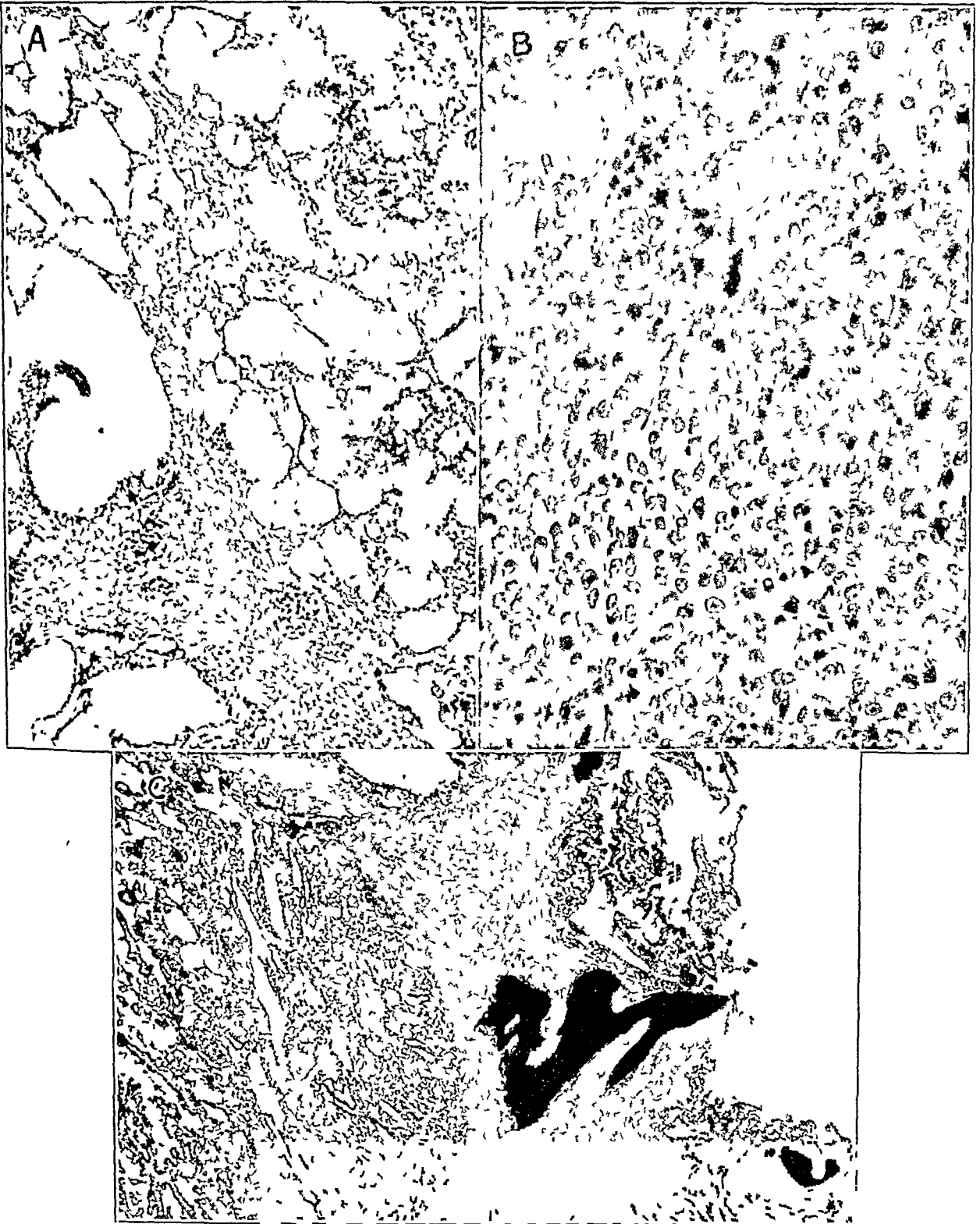


Fig 6—Angiosarcoma (A) Large spaces containing blood and protein material,  $\times 60$ , AIP neg no 102438, (B) cellular area with cluster of cells similar to capillary bed,  $\times 210$ , AIP neg no 102433, (C) area of invasion of bone,  $\times 40$ , AIP neg no 102434

limited to the conjunctiva. Only 4 occurred in patients less than 40 years of age. Of the 21 patients on whom clinical information is available, 11 complained of exophthalmos and 10 of a mass. Patients with anteriorly situated tumors sought medical assistance in most instances in less than five months after the mass was first noted, whereas in over one-half the cases in which exophthalmos was the initial complaint the symptoms had been present for more than one year.

Except for Hodgkin's disease and plasmacytoma, which can be separated histologically from the group, tumors of the lymphocytic series are classified with difficulty. Elsewhere in the body the integrity

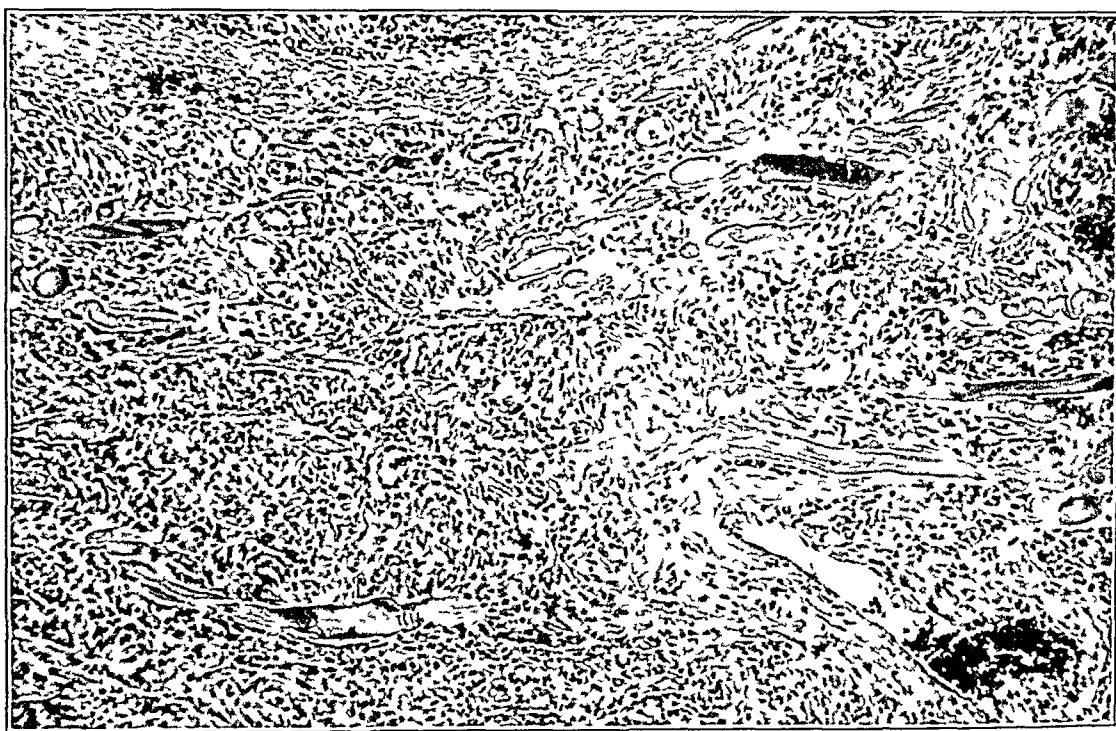


Fig 7—Hemangioendothelioma invading rectus muscle,  $\times 115$ , A I P neg no 104582

of the architecture of lymph nodes is an important criterion. In the orbit, however, nodes are not normally present, and the histologic distinction of lymphocytic infiltration, lymphatic lymphadenosis and benign and malignant lymphomatoid tumors about the eye is often difficult. The question of separating the benign from the malignant variety is further confused by the slow course of even some of the lymphosarcomas which may become multicentric, by the occasional "cure" of an isolated lesion of lymphosarcoma by excision and by the high radiosensitivity of both benign and malignant lymphomas. Unfortunately, the follow-up data on the cases in this series are too limited to be significant, although some of the information may be of interest

Four of the 25 excluded tumors were classified as "benign lymphomas" The age distribution and symptoms were not significantly different from those of the malignant lesions In these tumors the type cell was uniformly the small, mature lymphocyte, well formed or suggestive follicles were occasionally present

Although previously the differentiation of the types of lymphosarcoma has been labored, the growing impression among pathologists

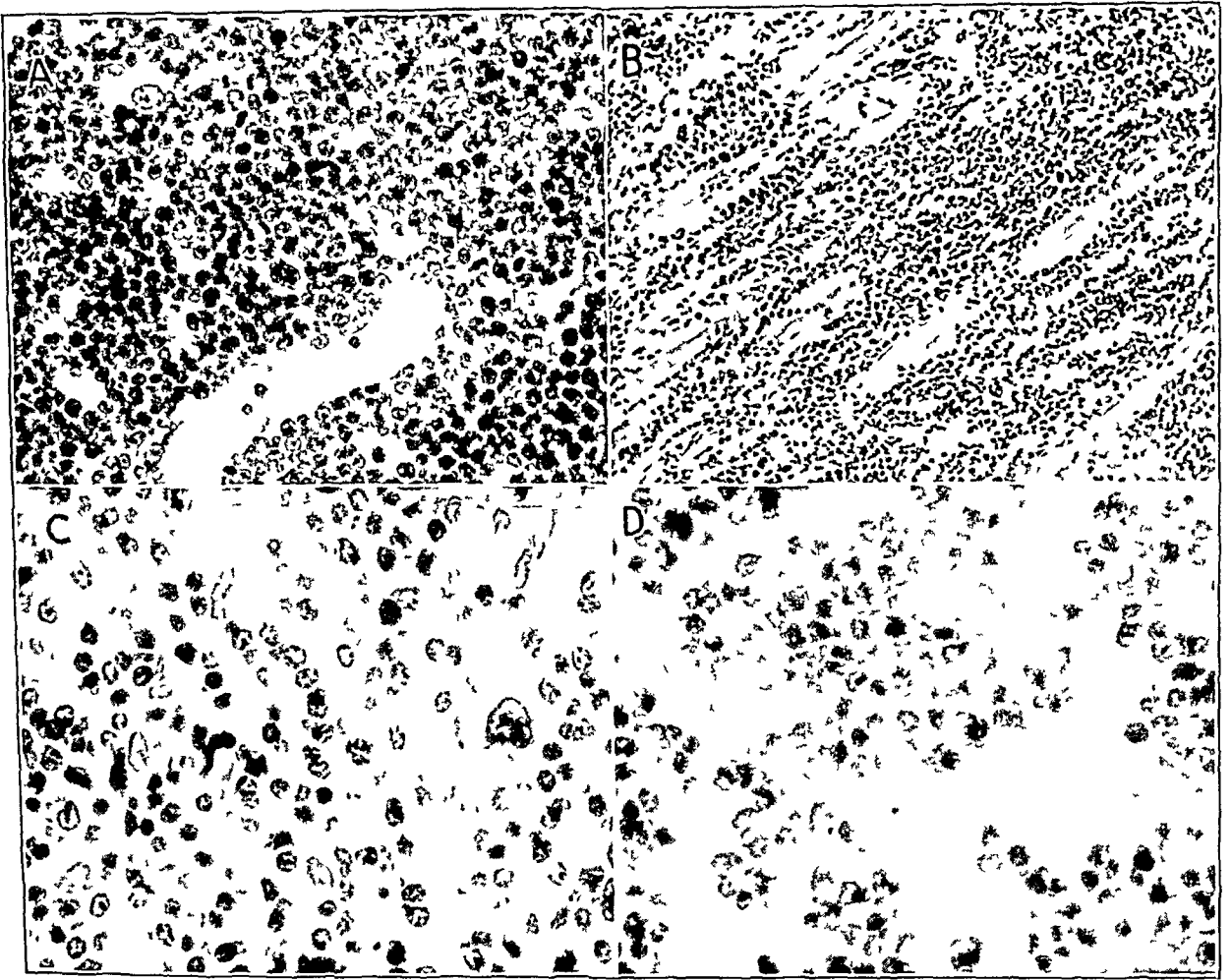


Fig 8—Hematopoietic tumors (A) Lymphosarcoma with mitotic activity,  $\times 475$ , AIP neg no 101231, (B) lymphosarcoma infiltrating muscle,  $\times 160$ , AIP neg no 101202, (C) Hodgkin's disease,  $\times 605$ , AIP neg no 104576, (D) plasmacytoma,  $\times 720$ , AIP neg no 104580

is that this delicate cataloguing is somewhat artificial, since several of the types appear to be merely stages of the same disease More than one type may be found in the same patient The term lymphosarcoma is used here to include the lymphoblastic, lymphocytic and reticulum cell varieties Eighteen tumors were included in the lymphosarcoma group In 2 cases there were abnormalities of the peripheral blood In 1 case the large mononuclear cells in the circulating blood



were interpreted by most of the Registry consultants as those of monocytic leukemia. In the second, lymphatic leukemia was associated with the orbital infiltration, which, as in all the other cases, was the only apparent site of disease at the time of operation. Histologically, these tumors were characterized by dense infiltrations of lymphocytes at different stages of maturation. Mitotic figures were common (fig 8A). Inconstant amounts of argyrophil reticulum were noted, and in the reticulum cell type an intimate relationship with the tumor cell was occasionally demonstrable. In many of the microscopic preparations lymphoid tissue invaded muscle and fat, indicating at least a locally invasive propensity (fig 8B).

There was 1 case of typical Hodgkin's disease. The Sternberg-Reed cell is shown in figure 8C. One tumor in the lymphomatoid group, characterized by pronounced pleomorphism, cells suggestive of the Dorothy Reed type and a peculiar desmoplastic reaction, was regarded as sclerosing Hodgkin's sarcoma.

The remaining tumor in this group was composed of sheets of mature plasma cells and was thought to be an isolated plasmocytoma (fig 8D). This was the only specimen which could be related to the myeloid series.

In this series, all the lymphomatoid tumors were, at least initially, isolated lesions. Evidence of generalized disease at the time the patient sought medical aid was noted only in the 2 instances in which an abnormal blood picture was described. It is now generally recognized that the leukemias may be merely other phases in the development of these diseases and that lymphosarcoma may occur with or without peripheral changes in the blood.

In this group of orbital lymphomas, death ensued in from two to nine months in 4 of the 7 cases in which the follow-up information was available. One patient, for example, had complained of increasing exophthalmos of five months' duration and died two months after operation, when generalized lymphadenopathy was noted. Two patients were well two and six years, respectively, after operation. One patient, with leukemia, was alive five years after operation with generalized glandular enlargement. No data were available in the other cases.

#### EPITHELIAL TUMORS

*Mixed Tumor of the Lacrimal Gland*—There were 25 mixed tumors of the orbit. They are included with the tumors of epithelial origin, since this concept of the histogenesis is most widely accepted, although others have been suggested.

The mixed tumor, which arises in the serous glands of the head, including the major and minor salivary glands, is included with orbital tumors by virtue of its occurrence in the lacrimal gland. McFarland

presented an excellent analysis of a group of these tumors of the salivary glands and a discussion of their nature<sup>1b</sup> The use of such terms as enchondroma, cylindroma, enclavoma, compounded tumor, endothelioma, basal cell carcinoma, sarcoma and epithelioma indicate the many histogenetic concepts More recently, the theory of the notochordal origin of these tumors, presented by Hellwig,<sup>2</sup> and the designation of muco-epidermoid tumors by Stewart and his associates<sup>3</sup> are noteworthy

In the 25 cases of this tumor the ages of the patients ranged from 18 to 76 years In 12 cases proptosis was the presenting complaint, in 9 it was of less than one year's duration, and in others it had been present for two, five and seven years, respectively In 13 other cases the presence of a noticeable mass was the initial symptom Such masses existed for from one to two years before surgical treatment The absence of tearing was noted in 1 case Roentgenograms were available in 2 cases, in 1 case they indicated erosion of the supraorbital ridge, and in the other, no bony change In 2 cases of recurrence erosion of bone was noted, and in 1 case there was massive invasion of the base of the cranium and the temporal fossa

Pathologically, all the specimens fulfilled the diagnostic criterion of being comprised of both epithelial and mesenchyma-like elements Eighteen of the tumors were considered typical and were composed of cuboidal epithelium and loose, chondromatoid connective tissue (fig 9 A) In the most differentiated variety, dilated acini and tubules, with walls usually made up of two layers of epithelium, were separated by lightly basophilic, fibrillar connective tissue, in which the cellular elements varied from spindle to stellate configuration This myxoid material and some of the contents of the glandular structures may stain red with mucicarmine In 5 specimens the presence of cystic spaces suggested the appearance of the Brooke type of basal cell carcinoma of the skin, the epithelioma adenoides cysticum (fig 9 B) Among other pathologic variants in 1 specimen, in addition to these cystic areas, there were large cellular sheets which were similar to those in the Krompecher type of basal cell carcinoma, or basaloma (fig 9 C) In 1 specimen, which was otherwise typical, keratin cysts were noted in the cellular areas (fig 9 D) The abrupt transition from epithelium to keratin and the presence of calcium were reminiscent of the calcifying

1b McFarland, J Three Hundred Mixed Tumors of the Salivary Glands of Which Sixty-Nine Recurred, Surg, Gynec & Obst **63**:457, 1936, Histopathologic Prognosis of Salivary Gland Mixed Tumors, Ann J M Sc **203** 502, 1942

2 Hellwig, C A Mixed Tumors of the Salivary Glands, Arch Path **40** 1 (July) 1945

3 Stewart, F W, Foote, F W, and Becker, W F Muco-Epidermoid Tumors of Salivary Glands, Ann Surg **122** 820, 1945

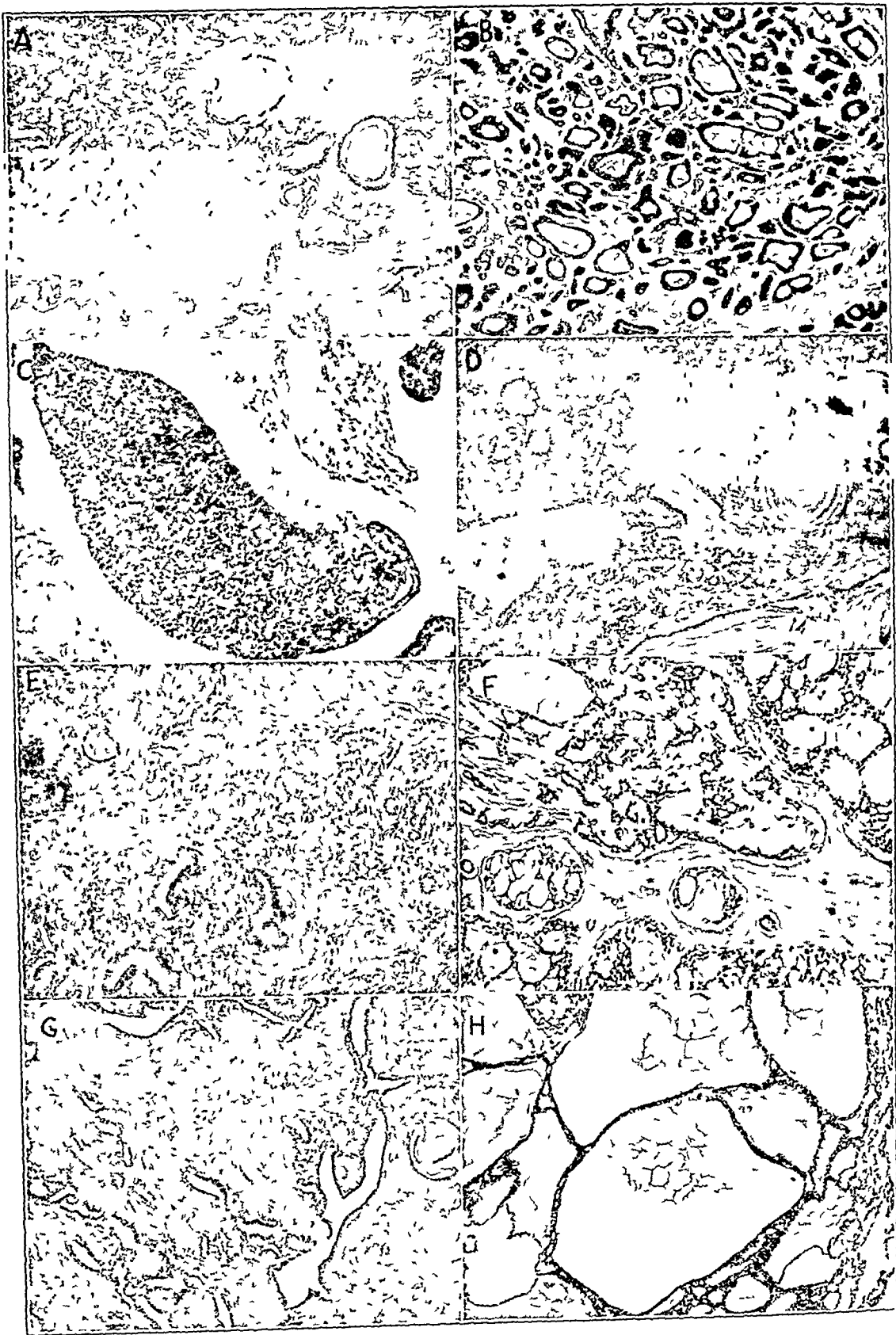


Fig 9—Mixed tumors (A) Archetype,  $\times 60$ , AIP neg no 100958, (B) tumor resembling epithelioma adenoides cysticum of the skin,  $\times 61$ , AIP neg no 100956, (C) tumor resembling Krompecher type of basal cell carcinoma,  $\times 60$ , AIP neg no 100955, (D) tumor with accumulations of keratin,  $\times 40$ , AIP neg no 100959, (E) tumor containing nests of cells similar to squamous cell pearls,  $\times 110$ , AIP neg no 104572, (F) tumor simulating colloid carcinoma of intestinal tract,  $\times 130$ , AIP neg no 104578, (G) tumor resembling carcinoma of adenofibroma of breast,  $\times 90$ , AIP neg no 104577, (H) tumor containing large cystic spaces,  $\times 90$ , AIP neg no 104575

epithelioma of the skin. In another specimen, cellular nests similar to epithelial pearls were observed (fig 9 E). One tumor, in which the mucinoid areas may have resulted from cellular degeneration (fig 9 F), was very much like the colloid carcinoma of the breast or intestinal tract. Another resembled the adenofibroma of the breast (fig 9 G). Large cystic spaces in the last specimen correlated with the cystic consistency noted clinically and accounted for the confusion with dermoid cyst (fig 9 H).

Numerous subclassifications based on the morphologic features of these tumors have been suggested, but there is little evidence that there is any real difference between the types, and in this series they were all classified as mixed tumors. Multiple sections often revealed at least small areas of the mixed tumor prototype, even though the initial sections were somewhat anomalous. McFarland<sup>1b</sup> stated that "histologic variations among mixed tumors have no bearing upon prognosis." He reported tumors classified histologically as sarcoma which behaved clinically in a manner identical with the usual mixed variety. In 1 of his cases the primary tumor was described as carcinoma, but the recurrent growth was noted by the same pathologist to be a more typically mixed tumor.

In most of the cases in this group treatment was by simple excision of the tumor initially, but in at least 8 cases enucleation or exenteration was finally required.

Follow-up data are available in less than one-half the cases. In only 1 of these 10 cases was there no evidence of recurrence five years after operation, and in 9 cases a second operation was required within one to six years after the first. The records in 4 cases indicated only the initial recurrence, second recurrences were noted in 5 cases. Recurrence in 1 of the cases of morphologically typical tumor was first noted fifteen months after operation, and the neoplasm was removed three months later. In some areas of this mass there were cells containing an abundance of eosinophilic cytoplasm and large, nucleolated nuclei suggestive of squamous epithelium. Occasional bizarre forms, including multinucleated cells, were noted. The connective tissue stroma, composed of young fibroblasts, had lost its basophilic, myxoid appearance and represented merely the desmoplastic response to the epithelial growth (fig 10 A). This was morphologically a squamous cell carcinoma arising in a typical mixed tumor.

McFarland reported a tumor with chondroid features in some areas and cellular structure typical of carcinoma in others. At autopsy only the histologically malignant moiety was noted in the metastatic masses. Sanders<sup>4</sup> also showed that only the epithelial constituent was present

<sup>4</sup> Sanders, T. E. Mixed Tumors of the Lacrimal Gland, *Arch Ophth* **21** 239 (Feb.) 1939

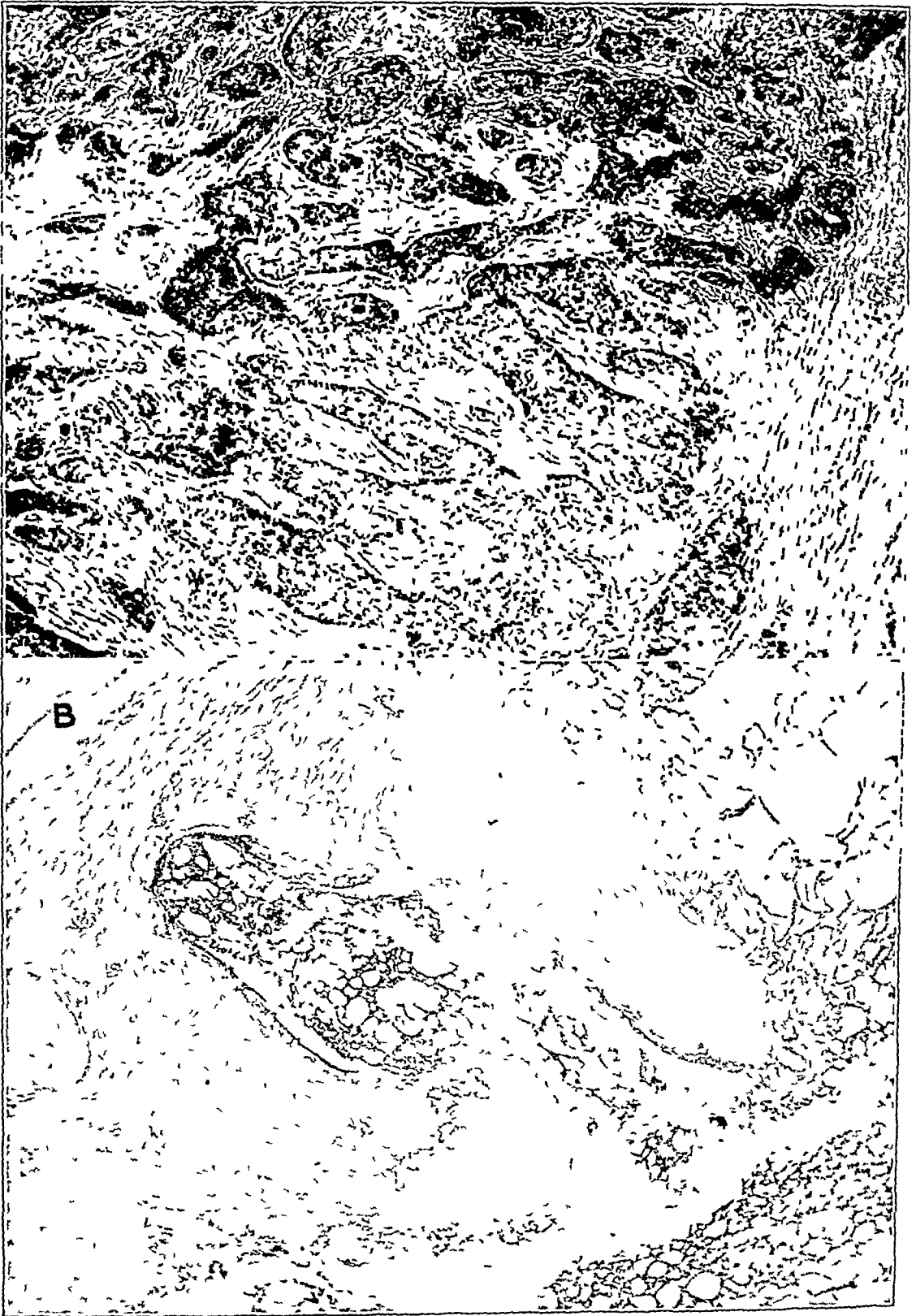


Fig 10—Mixed tumor. (A) Recurrence resembling squamous cell carcinoma,  $\times 62$ , AIP neg no 100957, (B) tumor cells invading capsule,  $\times 55$ , AIP neg no 104574

characteristics of neurofibroma were noted: abortive Verocay bodies, serpentine fibers and edema (fig. 12 *A*). In a case of von Recklinghausen's disease (multiple neurofibromatosis) an orbital neurofibroma was present.

*Meningioma.*—Seventeen of the tumors in this series arose in the arachnoid which invests the brain and the optic nerve. Whether this sheath is of epiblastic or mesoblastic origin is controversial, although the cells, in their ability to produce bone and cartilage, unquestionably behave like mesenchymal tissue.

Since the work of Schmidt,<sup>5</sup> in 1902, it has been generally believed that intracranial meningiomas arise in the arachnoidal granulations. Analogous clusters of arachnoidal cells, which may eventually form psammoma bodies, are to be seen in normal optic nerve sheaths, and it is assumed, therefore, that some orbital meningiomas may arise from such clusters (fig. 12 *B* and *C*). Cushing and Eisenhardt<sup>6</sup> presented an excellent discussion of the subject, including the histogenesis.

A meningioma may involve the orbit in any of three ways: First, it may be primary in the sheath of Schwalbe; second, it may extend into and involve the sheath through the optic foramen from a site of origin in the basilar meninges, or, third, it may invade the orbit through the bony wall, usually the roof, without involving the coverings of the optic nerve.

From the therapeutic point of view, it is obviously of cardinal importance to know whether a tumor is entirely intraorbital or partly intracranial. Verhoeff<sup>7</sup> previously expressed the opinion that no case of primary intraorbital meningioma had been satisfactorily demonstrated. This is in agreement with evidence presented earlier by Pagenstecher,<sup>8</sup> in 1902, and by Dusaussay,<sup>9</sup> in 1875, each of whom reported a case of meningioma of the optic nerve in which small intracranial masses were observed at autopsy many years after orbital operation. In Dusaussay's case, the interval from operation to death was twenty-five years.

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5. Schmidt, M.: Ueber die Pacchionischen Granulationen und ihr Verhältniss zu den Sarcomen und Psammomen der Dura mater, Virchows Arch. f. path. Anat. **170**:429, 1902.

6. Cushing, H., and Eisenhardt, L.: Meningiomas: Their Classification, Regional Behavior, Life History and Surgical End Results, Springfield, Ill., Charles C Thomas, Publisher, 1938.

7. Verhoeff, F. H.: Tumors of the Optic Nerve, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1027.

8. Pagenstecher, A.: Ueber Opticustumoren, Arch. f. Ophth. **54**:300, 1902.

9. Dusaussay: Sarcome angiolithique du nerf optique gauche, Bull. Soc. anat. de Paris **10**:211, 1875.

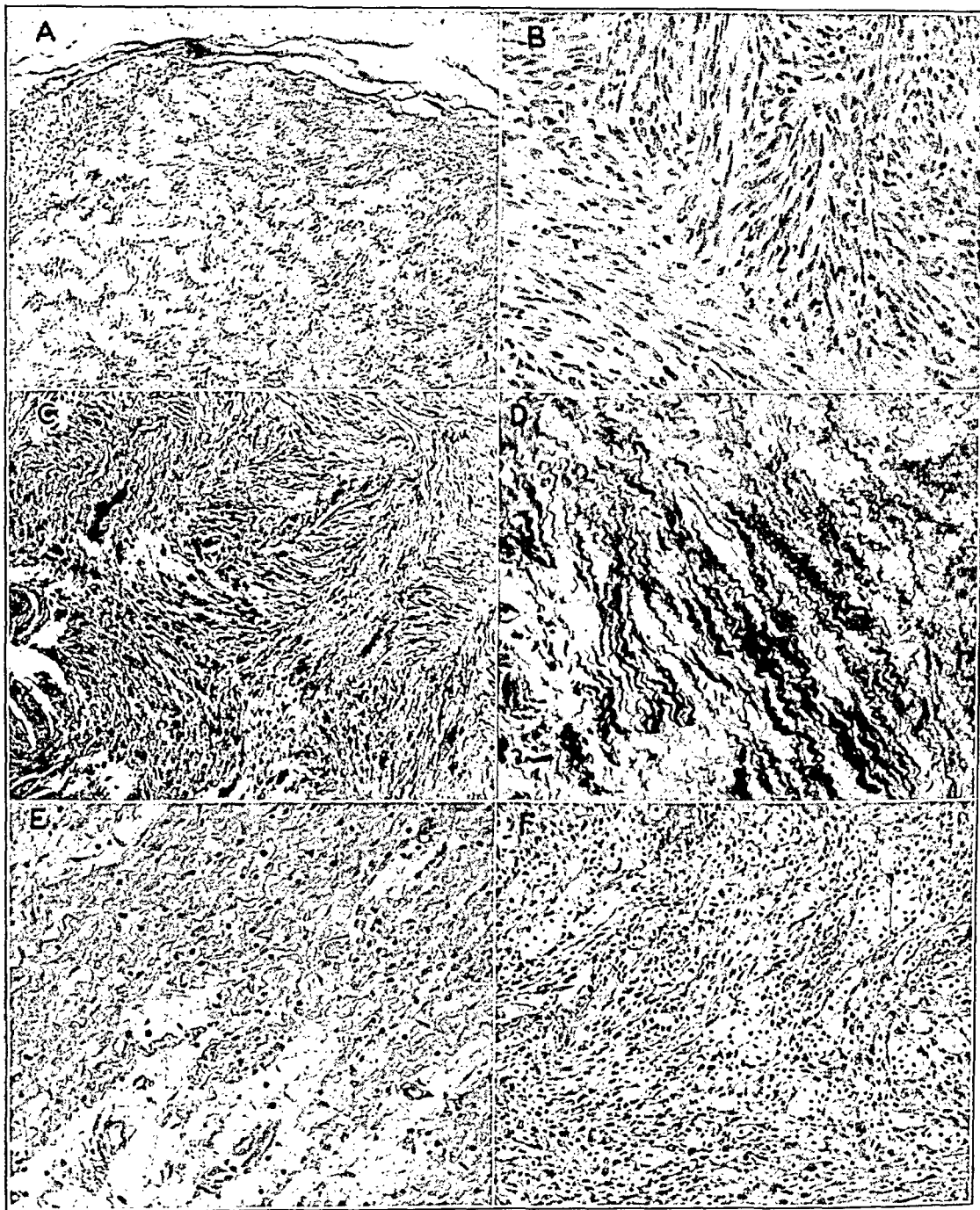


Fig. 11.—Neurofibroma. (A) Palisades of cells,  $\times 80$ , A.I.P. neg. no. 100896; (B) herringbone arrangement,  $\times 235$ , A.I.P. neg. no. 101283; (C) mild anaplasia,  $\times 120$ , A.I.P. neg. no. 100894; (D) serpentine collagen fibers (Van Gieson stain),  $\times 220$ , A.I.P. neg. no. 100895; (E) edematous tumor,  $\times 150$ , A.I.P. neg. no. 100889; (F) xanthoma cells,  $\times 115$ , A.I.P. neg. no. 101288.

(1933), Love<sup>12</sup> (1935) and Aebli<sup>13</sup> (1945). Such lesions are, of course, primary in the cranium, generally arising in the olfactory groove or the sphenoidal ridge and extending into the orbit through the dura and bone.

Cushing and Eisenhardt described a case, reported to them by Friedenwald, which was thought to demonstrate conclusively, on the basis of the presence of a normal optic nerve sheath central to the tumor and of roentgenologic evidence indicating integrity of bone, that primary meningiomas of the optic nerve sheath do occur.

It is clear, then, that intraorbital meningioma may occur with or without an intracranial meningioma; if both the orbit and the cranial cavity contain tumors, either may be the primary site. If there is any evidence that the tumor is not confined to the orbital cavity, craniotomy is mandatory.

In this series of 17 cases of meningioma, 40 years was the median age. In 3 patients, or almost 20 per cent, the patient was under 14 years of age. In 12 cases information concerning symptoms was available, and in 9 of these the initial symptom was exophthalmos, which had been present for an average of five years. In 1 case there was a complaint of decreasing vision for three years and of exophthalmos for the last two years, an order of symptoms the reverse of that ordinarily encountered in cases of orbital meningioma. In 2 cases the tumor was incidentally encountered at pathologic examination of the globe after enucleation for the ocular pain of absolute glaucoma secondary to chronic iridocyclitis. In addition to exophthalmos, loss of vision was noted in 3 cases. In 2 instances, diminution of vision accompanied the exophthalmos, and in the third it had been noted only six months, although proptosis had been present for several years. Exophthalmos, then, was recorded in a total of 10 cases; its absence was noted in 2 cases, and there was no pertinent statement in 5 cases.

In 2 cases there was swelling of the lids. Chemosis was noted in 3 cases. A clinically palpable mass was observed in 1 case, a finding which is, of course, unusual with the posteriorly situated meningioma. Specific mention of abnormal ocular movements was made in only 3 cases. There were limitation of external rotation in 2 cases and total immobility in another, in which the tumor filled the orbit. In 9 cases the location of the meningioma was described. In 4 it surrounded the nerve; in 1 it filled the orbit; in 3 it was in the outer portion of the orbit, and in 1 it was noted superiorly.

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12. Love, J. G.: Transcranial Removal of an Intraorbital Meningioma, *Proc. Staff Meet., Mayo Clin.* **10**:213, 1935.

13. Aebli, R.: Meningioma of the Sphenoidal Ridge: Report of a Case, *Arch. Ophth.* **33**:86 (Jan.) 1945.





Fig. 12.—(A) Neurofibroma, with abortive Verocay bodies, serpentine fibers and edema,  $\times 90$ , A.I.P. neg. no. 104515; (B) normal arachnoid cells with cell clusters,  $\times 55$ , A.I.P. 100539; (C) normal optic nerve with psammoma bodies in arachnoid,  $\times 50$ , A.I.P. neg. no. 100525.

Cases of intraorbital meningioma without involvement of the optic nerve sheath were reported by de Schweinitz<sup>10</sup> (1914), Bailey<sup>11</sup>

10. de Schweinitz, G. E.: Psammosarcoma of the Orbit in a Girl of Thirteen: Successful Removal with Preservation of the Eyeball and Its Functions, *Tr. Am. Ophth. Soc.* **13**:617, 1914.  
 11. Bailey, P.: *Intracranial Tumors*, Springfield, Ill., Charles C Thomas, Publisher, 1933.

which the central nuclear substance had been lost. Mitotic figures were rare, and there was no hyperchromatism. The second type, represented by 8 specimens, differed from the meningothelial type only in the alveolar grouping of the cells within delicate fibrous stroma (fig. 13 *B*). In the third type, represented by 6 specimens, the cellular arrangement was less orderly, and psammoma bodies and whorls were prominent. In figure 13, *C* shows the whorls; *D*, the early hyalin masses, with a few nuclei yet remaining, and *E*, the fully developed psammoma bodies.

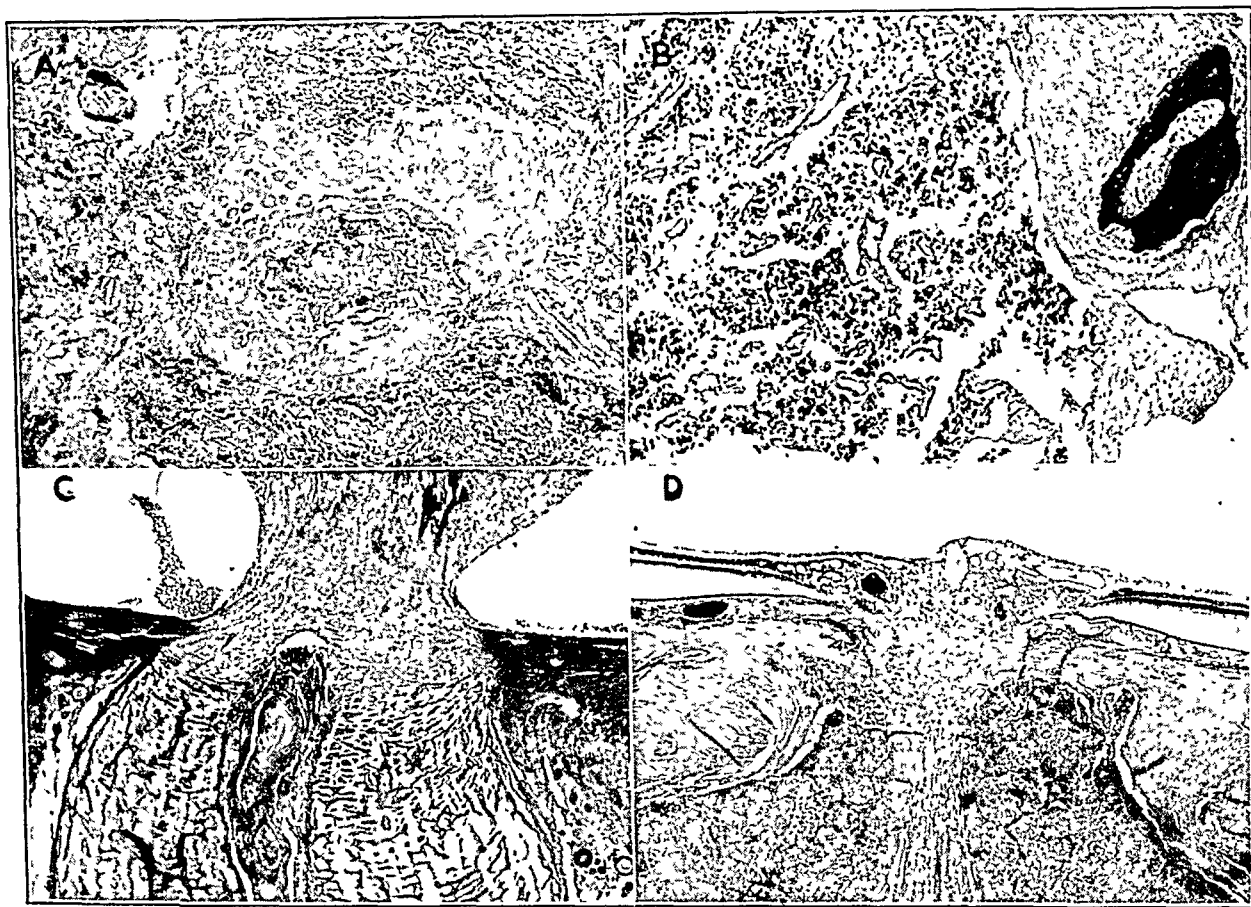


Fig. 14.—Meningioma. (*A*) Bone proliferation and/or invasion,  $\times 75$ , A.I.P. neg. no. 100535; (*B*) infiltration of extraocular muscle,  $\times 50$ , A.I.P. neg. no. 100532; (*C*) extension along central vessels in optic nerve,  $\times 15$ , A.I.P. neg. no. 100529; (*D*) invasion of nerve head (Coston, A. O.: Primary Tumor of Optic Nerve, with Report of Case, Arch. Ophth. **15**:696 [April] 1936),  $\times 20$ , A.I.P. neg. no. 100540.

In the 1 specimen of the fourth type, the cells were more epithelioid and robust; strands of cells were separated by thin-walled vascular channels, a feature not noted in the other specimens.

In no instance was there microscopic evidence of a fibrous capsule; the tumors were, in general, locally invasive. The neoplasm often infiltrated orbital fat, and in 1 case the presence of bone and periosteum indicated probable infiltration of the orbital wall, with associated osseous

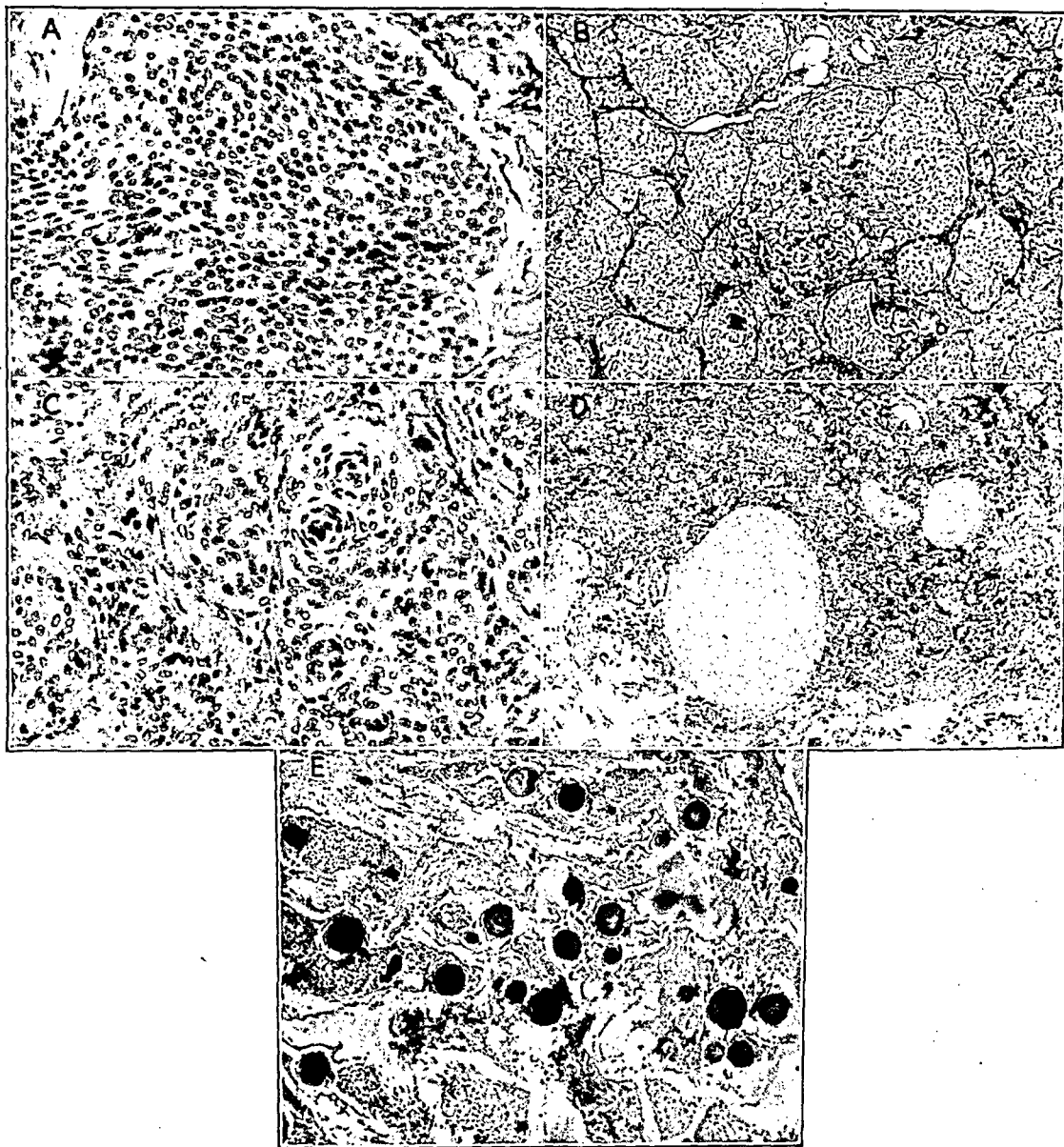


Fig. 13.—Meningioma. (A) Meningothelial type,  $\times 285$ , A.I.P. neg. no. 100536; (B) alveolar type,  $\times 50$ , A.I.P. neg. no. 100533; (C) cellular whorls,  $\times 285$ , A.I.P. neg. no. 100537; (D) early psammoma bodies,  $\times 55$ , A.I.P. neg. no. 100538; (E) calcifying psammoma bodies,  $\times 55$ , A.I.P. neg. no. 100524.

Histologically, the meningiomas were of four types. The first, or meningothelial type, of which there were 2 specimens, was characterized by syncytial sheets of cells, uniformly distributed (fig. 13 A). Oval to round, vesicular nuclei were noted, which contained moderate amounts of chromatin and an occasional dark-staining nucleolus. The cells had scarcely distinguishable boundaries but appeared to be uniform in size and shape. An occasional nucleus was represented only by a shell from

if intracranial tumor is later noted it may be successfully removed. Primary transcranial approach would, of course, expose an associated intracranial tumor. In cases in which more conservative surgical procedures on the orbit are contemplated, roentgenologic, pathologic and functional studies become even more important in ruling out tumors within the calvaria.

*Glioma.*—Five of the orbital tumors were a result of enlargement of the optic nerve in which the increase in size was due primarily to neoplastic proliferation of the supporting tissue of the nerve, the glial network.

A patient 15 years of age was the only one with glioma of the optic nerve occurring beyond the first decade of life. In all cases exophthalmos was the presenting symptom, with a duration of from two to four years. Decrease in vision was invariably noted, but in the 2 instances in which its duration was indicated it had made its appearance more recently than the proptosis.

Although there is similarity between the symptoms of glioma and those of meningioma, the age of the patient will usually serve as a distinguishing factor. No rigid criterion can be enunciated, but in general it may be accepted that the older the patient the greater the probability that the tumor is a meningioma.

Grossly, the tumors were described as from the size of a cherry to that of a walnut. Microscopically, attenuated connective tissue septums separated bundles of nerve tissue in which the glial element, particularly astrocytes, had proliferated (fig. 15 *A*). In the nerve adjacent to the pronounced tumefaction, similar hyperplastic changes of milder degree were present. Verhoeff<sup>14</sup> described a peculiar arachnoidal proliferation which suggests primary meningioma (fig. 15 *B*). The swelling did not extend to the optic papilla in any of the cases in this group.

In all cases treatment was by enucleation with excision of the tumor. Significant follow-up information was available in only 1 case; the patient was well five years after operation. Verhoeff<sup>14</sup> indicated that incomplete excision of these tumors has resulted in regression of the remaining mass, so that complete excision may be less important than in the case of the meningioma, the other intraorbital tumor, with which intracranial lesions may coexist. In at least 1 case the tumor was noted to extend through the optic foramen.

*Neurofibrosarcoma.*—Nine tumors were comprised of spindle-shaped cells which were producing collagen. In spite of varying degrees of anaplasia, moderate palisading and fasciculation (fig. 15 *C*) were dis-

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14. Verhoeff, F. H.: Primary Intraneural Tumor of the Optic Nerve, Arch Ophth. 51:239, 1922.

hyperplasia (fig. 14 *A*). Voluntary muscle was invaded in several specimens (fig. 14 *B*). In 1 instance the tumor extended along the central retinal vessels within the optic nerve (fig. 14 *C*). In 1 case the tumor invaded the retina at the disk (fig. 14 *D*).

In 6 of the 8 cases in which roentgenographic studies were made, no abnormalities were observed; in 1 case thickening of the external wall was noted, which at operation was characterized as osteomatous. In this case a radiopaque, soft tissue mass was reported. In this specimen, no psammoma bodies were observed in the sections examined. Psammoma bodies were noted in great numbers in 1 case and were sparsely distributed in another of the 6 cases in which roentgenologic examination was reported as showing nothing abnormal. The presence of psammoma bodies in random microscopic sections does not correlate with radiopacity, although it is assumed that heavy depositions of calcium would be apparent roentgenographically. The roentgenogram did not reveal the moderate orbital erosion which was observed at operation in 1 case.

In 11 of the 12 cases of meningioma in which operation was described, the procedure was enucleation with excision of the tumor. In 1 of these cases, because of the subsequent onset of marked swelling of orbital soft tissue, the orbit was exenterated and a large amount of tumor tissue was removed. In a second case, a small intracranial mass was noted five years after enucleation at a second operation by a neurosurgeon. In only 1 of the 12 cases was the Krönlein operation performed. The tumor was described as having been entirely within the orbit, but five months after operation there were total blindness and intense swelling of the lid. An osteoplastic craniotomy was performed, disclosing a meningioma of the anterior and middle fossae.

In 9 cases there was no evidence of recurrence at intervals ranging from six months to twenty-one years after operation. In only 1 of the 2 cases in which an intracranial lesion was demonstrated were follow-up data available. In this instance the patient was well eight years after the original operation and three years after craniotomy. The delayed discovery of the intracranial tumor apparently did not vitiate the possibility of an eventual favorable result. No follow-up data were available in 7 cases. One of the cases in which the existence of intracranial tumor was established by operation was among the 3 in which pre-operative irradiation was given.

In summary, tumors of the meninges observed within the orbit occurred in patients representing a broad age distribution, from 8 to 83 years. The patients usually noted slowly progressive exophthalmos with gradual loss of vision. On the basis of the cases studied, it appears that enucleation with excision of the tumor may be adequate, and that

tinguishable; this cellular disposition suggested that the tumor was related to nerve and probably arose in the nerve sheath, or so-called perineural connective tissue.

The age of the patients varied from 4 to 71 years, and there was not the preponderance of young patients noted in the group of mesenchymal sarcomas. Follow-up data were available in 6 cases. Two patients were alive and well two and four years, respectively, after operation. Two other patients were alive ten months and five years after operation, but recurrence had been noted clinically at ten months and three years, respectively. The 2 recorded deaths occurred one and two years after operation, the first with at least local evidence of recurrence and the second with evidence of metastasis to the lung. It would appear that the prognosis of neurogenic sarcoma is not different from that of other malignant tumors originating in mesenchymal tissue.

#### DEVELOPMENTAL FAULTS

Eighteen tumors in this series originated in developmental abnormalities; 17 were dermoid cysts and 1 was a teratoma. Both these neoplasms are regarded as congenital and as resulting from the inclusion of dermoid tissues along the lines of embryonic fissure. In spite of the congenital nature of these tumors, symptoms often do not appear for several years, and probably result from episodes of increased growth and secretory activity of the lining cells. Presenting symptoms in the present series were related to a "mass in the orbit" and varied in duration from five months to over twenty years. The average age was 22 years, the extremes being 17 months and 46 years. In only 2 infants and 3 adolescents had the masses been noted from birth.

In all but 1 case, the lesion presented anteriorly and was simply excised. In the exceptional case, a woman aged 46 had exophthalmos of three years' duration, associated with decreasing vision. The dermoid and an osteoma of the external wall of the orbit were removed by the Krönlein operation.

The dermoids were cystic masses with cavities measuring as much as 2 cm. in diameter. They were usually filled with a pultaceous material, comprised of fatty, keratic debris containing hair fibers (fig. 16 *A*). The cavities were lined by squamous epithelium with a surrounding connective tissue stroma, through which the appendages of the skin reached the cyst (fig. 16 *B*). The thick squamous cell lining had often been destroyed, probably by pressure and repeated inflammation, and the walls had become hyalinized (fig. 16 *C*). Cellular reaction to the lipids included lipidic histiocytes and epithelioid and giant cells. Calcific deposits were present in some areas. The thickness of the wall varied from several millimeters to a fraction of a millimeter, the

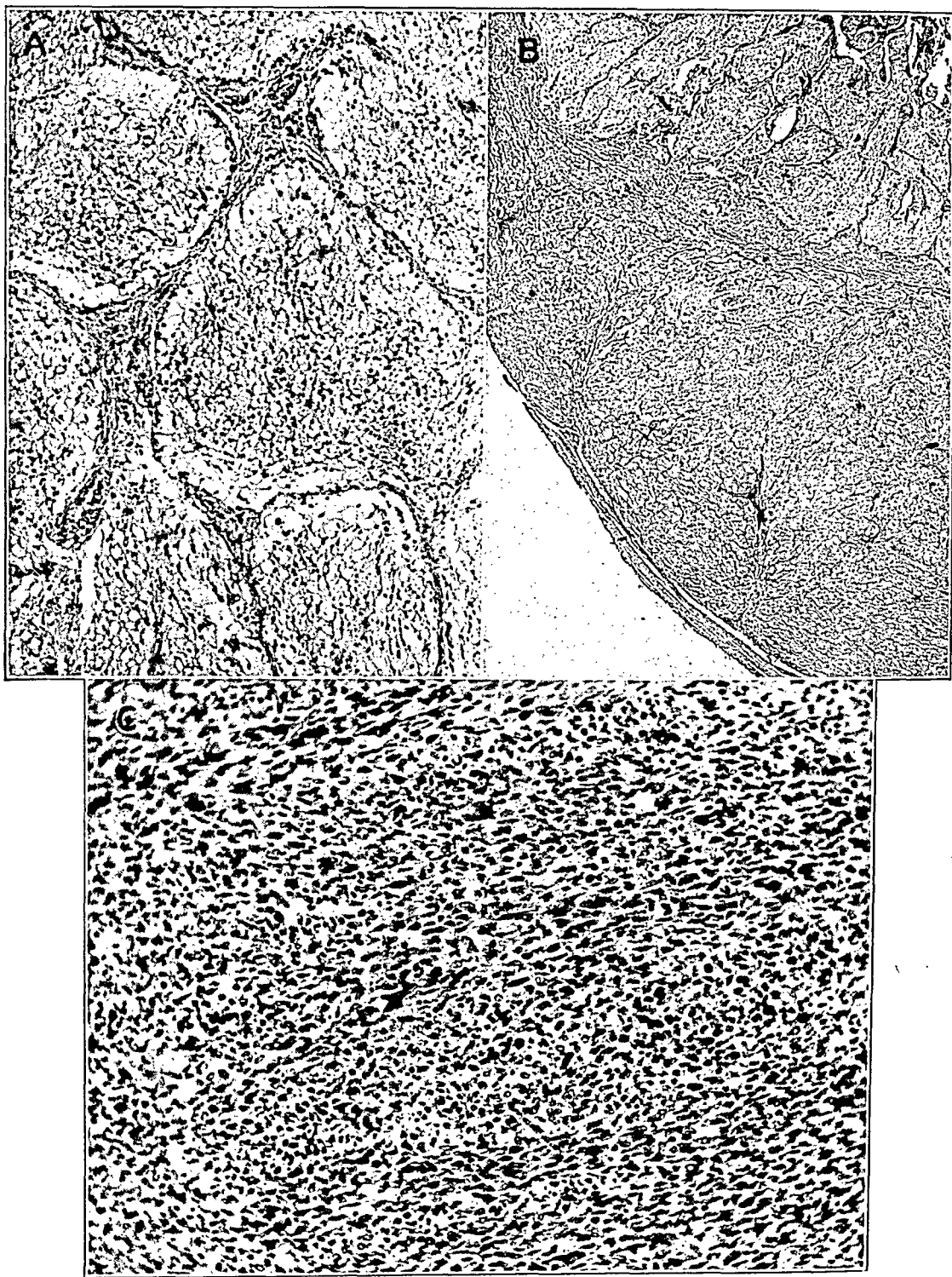


Fig. 15.—(A-B) Glioma of optic nerve. (A) Thickened nerve bundles,  $\times 90$ , A.I.P. neg. no. 101312; (B) associated arachnoidal proliferation,  $\times 17$ , A.I.P. neg. no. 101314; (C) neurogenic fibrosarcoma with fasciculation of cells,  $\times 210$ , A.I.P. neg. no. 104517.



nerve and muscle in many sections indicated the difficulty of dissecting even the innocuous dermoid from the orbit without at least minor destruction. Many locules were observed in a specimen (fig. 16 C) taken from a boxer, whose orbit had been exposed to repeated trauma. Gifford<sup>15</sup> commented on the extensive ramification of some dermoids, making extirpation difficult and accounting for the frequency of recurrence. In at least 5 of the cases in this group there had been a previous operation, but in only 1 was it recorded as excision of the mass. In 1 instance at least the cyst was attached to periosteum (fig. 16 D), and the surgeon removed adjacent bone, which grossly appeared to have been involved. Stout<sup>16</sup> stated that intraorbital dermoids may erode outward and that dermoid cysts of the skull and facial bones may erode into the orbit. None in this series was of that nature. In 1 instance a portion of lacrimal gland to which the cyst adhered was removed with it (fig. 16 E). The presence of cartilage, in addition to the dermoid elements, in 1 specimen led to a pathologic diagnosis of teratoma (fig. 16 F).

#### SECONDARY TUMORS

The 38 tumors which were secondary in the extraocular orbit were of five histologic types.

*Carcinoma.*—Twenty-four tumors were malignant epithelial growths arising outside the orbit. The average age of the patients was 58 years. Exophthalmos was a presenting complaint in 6 cases and was noted with primary tumor of the breast in 3 cases, with squamous cell carcinoma, probably arising from the sinuses, in 2 cases, and with conjunctival carcinoma in 1 case. In the last case the tumor had arisen in the superior fornix, but apparently its extension into the orbit was more rapid than the growth of the primary tumor. The presence of an anteriorly situated mass was the initial complaint in 8 cases, including 5 cases in which the primary tumor was in the adjacent skin, 1 case in which it was in the conjunctiva, 1 case in which it was in the nasolacrimal duct and 1 case in which it was metastatic from the large intestine. Loss of vision was noted in 1 case and was related to an associated tumor in the maxillary sinus.

In 17 cases the tumor had invaded the orbit from an adjacent site; it resulted from hematogenous dissemination in 4 cases, and the origin was not established in 3 cases. Of the locally arising tumors, a squamous cell carcinoma had invaded the orbit from the adjacent nasal sinuses in 5 cases (from the antrum in 3 and from the ethmoid cells in 2 cases). The origin of an orbital adenocarcinoma was suggested by

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15. Gifford, H.: Recurrent Dermoid Cyst: Successful Treatment with Trichloroacetic Acid, *Arch. Ophth.* 2:305 (Sept.) 1929.

16. Stout, A. P.: *Human Cancer*, Philadelphia, Lea & Febiger, 1932.



thin wall accounting for difficulty in removing several of the dermoids without rupture.

The surrounding connective tissue was often vascular and contained numbers of plasma cells and lymphocytes. The inclusions of orbital

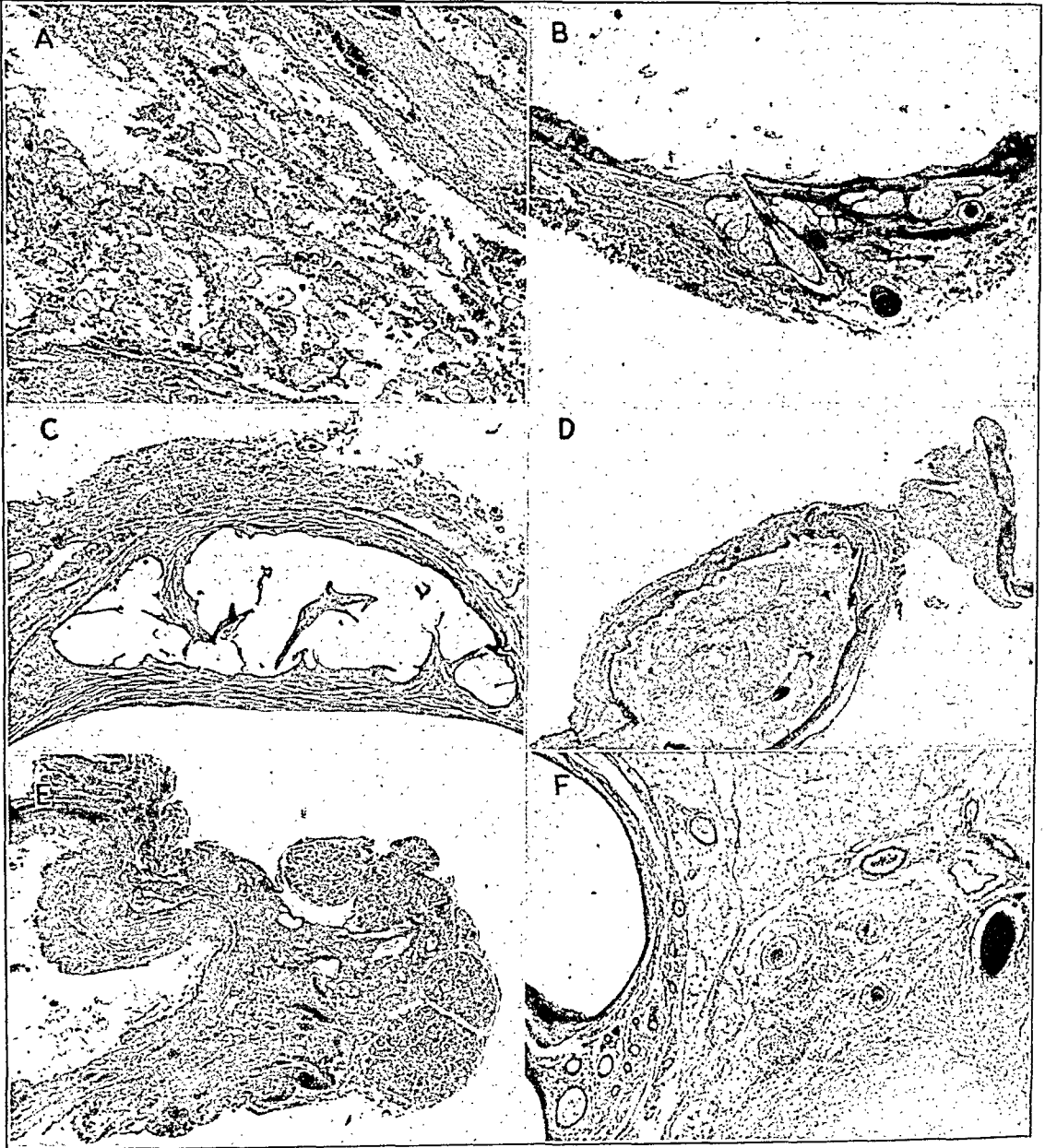


Fig. 16.—Dermoid cyst. (A) Hair shafts and keratic debris,  $\times 55$ , A.I.P. neg. no. 100526; (B) hair follicle, sebaceous glands and calcium deposits,  $\times 15$ , A.I.P. neg. no. 100528; (C) multilocular cyst with hyalinized lining,  $\times 10$ , A.I.P. neg. no. 100530; (D) adherent periosteum and bone,  $\times 15$ , A.I.P. neg. no. 100532; (E) proximity to lacrimal gland,  $\times 15$ , A.I.P. neg. no. 100527; (F) teratoid tumor containing epithelial cysts, hair shafts and cartilage,  $\times 40$ , A.I.P. neg. no. 101313.

wall. Its probable origin in the gastrointestinal tract was suggested by its microscopic appearance before the discovery of the primary tumor.

All the 15 replies to follow-up inquiries reported the death of the patient. The 12 deaths from tumor in from four months to three years indicated the intrinsic severity of tumors which extended or metastasized, and the 3 deaths from other causes were related to the age of patients with carcinoma.

*Neuroblastoma.*—The ages in the 6 cases of intraorbital neuroblastoma ranged from 2 months to 13 years. In one-half the cases exophthalmos was the presenting symptom and had been noted from five to sixteen months. In the other 3 instances the lesions were anteriorly situated and had been present for periods of three to nine weeks.

The postoperative interval was sufficiently great to warrant follow-up investigation in only 3 of the cases. In 1 of these, the patient was alive one year after exenteration, but there was evidence of local recurrence and of an intracranial lesion. Autopsy in the other 2 cases revealed a primary tumor in only 1, and in that case it occurred in the adrenal gland. In the other case it was assumed that a retroperitoneal or other paravertebral sympathetic ganglion was the parent focus.

The differentiation of this tumor histologically (fig. 17 *B*) from other morphologically similar neurogenic tumors, e. g., the retinoblastoma, is often difficult, and the ophthalmologist's statement that intraocular tumor is not present is important. The diagnosis can be considered conclusive only when the primary tumor is found.

*Malignant Melanoma.*—The large numbers of epibulbar extensions of choroidal tumors having been excluded from consideration, 6 cases of intraorbital malignant melanoma remain. In 4 of these cases the tumor contained no pigment in the sections examined and was cytologically of the type which in the choroid would be classified as epithelioid (fig. 17 *C*). In 1 of the cases the initial complaint had been that of an enlarged inguinal lymph node, and by the time of enucleation there was generalized lymphadenopathy. Pathologic examination of the ipsilateral eye revealed no intraocular tumor. The eyes in the other 3 cases were not available for inspection.

The fifth case was one of a pigmented tumor which would be classified as a mixed cell type. Autopsy revealed extensive generalized metastases, but both eyes were free of tumor. The grossly suspicious lesions of the skin proved histologically to be benign. No other possible primary source was found. Only in the sixth case was the orbital mass related to an intraocular melanoma, for which enucleation had been performed seven months previously.

roentgenologic examination to have been the maxillary sinus. A squamous cell carcinoma had invaded the orbit from the surrounding skin in 1 case, and a basal cell carcinoma, in 4 cases. The lacrimal sac and the nasolacrimal duct contributed an adenocarcinoma and squamous cell carcinoma, respectively (fig. 17 *A*). Squamous cell carcinoma had arisen in the conjunctiva in 2 cases; the site was not stated in 2 others, but it is likely that they were local. The metastatic orbital masses were primary in the female breast in 3 cases and in the colon in 1 case. A glandular carcinoma and 2 undifferentiated carcinomas were

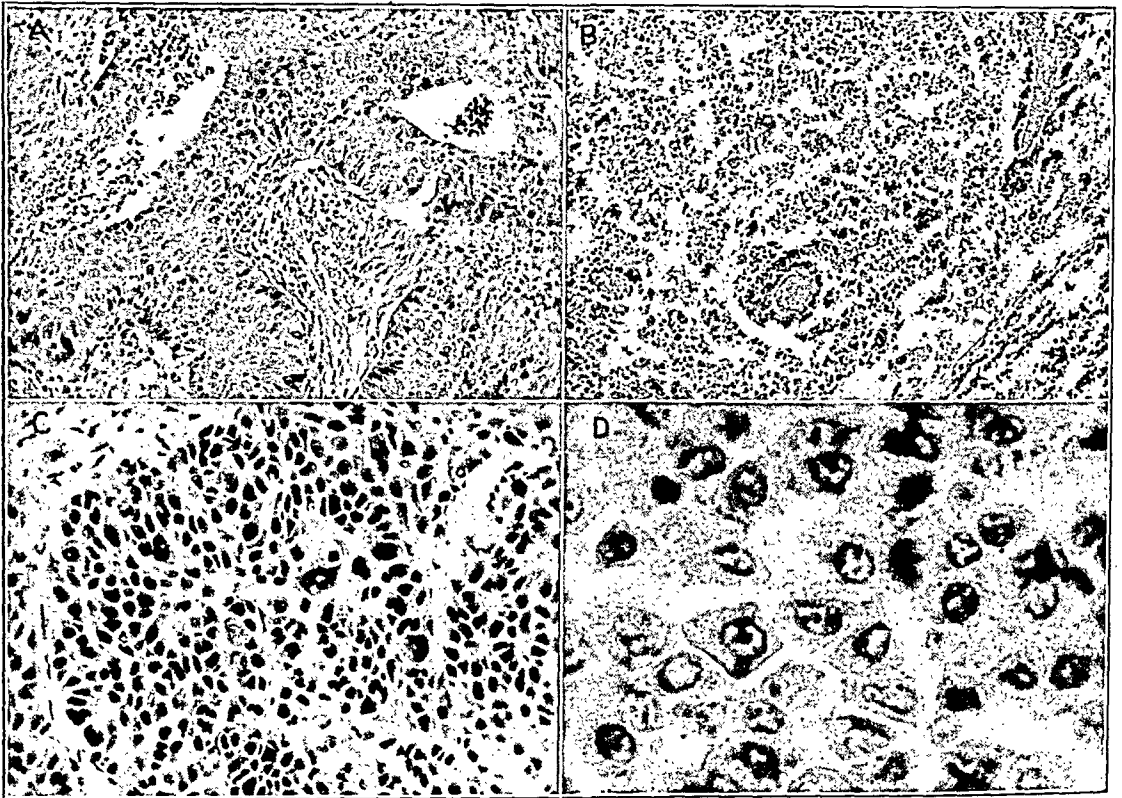


Fig. 17.—Secondary orbital tumors. (*A*) Squamous cell carcinoma arising in nasolacrimal duct,  $\times 160$ , A.I.P. neg. no. 101315; (*B*) metastatic neuroblastoma, showing perivascular cuffs of cells,  $\times 98$ , A.I.P. neg. no. 101316; (*C*) malignant melanoma,  $\times 317$ , A.I.P. neg. no. 101317; (*D*) pituitary adenoma,  $\times 1,000$ , A.I.P. neg. no. 102437.

of undetermined origin. In 1 case widespread metastases were already present at the time of operation; in a second, the tumor in the breast was discovered only after the orbital mass had been removed by the Krönlein operation. Similar information was not available concerning the other case.

The tumor metastatic from the colon was situated anteriorly in the orbit and was adherent to the periosteum of the superior orbital

## ABSTRACT OF DISCUSSION

DR. GEORGIANA DVORAK-THEOBALD, Oak Park, Ill.: As Dr. Forrest has pointed out, correlation of clinical data with histologic features is of particular importance in the case of orbital tumors, since, more than is true of most ophthalmic disease, the treatment and prognosis are determined by microscopic changes. Moreover, it seems that the textbooks and encyclopedias present the material on orbital tumors in a much more hit-or-miss manner than that on other pathologic states; hence, we are particularly indebted to Dr. Forrest for his clearcut classification of these tumors according to their origin in the various types of orbital tissue. It is of particular importance that there be a good basic classification now that the literature on these tumors is increasing rather rapidly, and there should be some consistency of nomenclature. With increased standardization of terminology, there will, perhaps, be less variation in reported incidence of the various types than is true now. A check of the articles by Benedict and others and a visit to Dr. Ingall's exhibit in the present Session will make clear the rather wide differences in terminology.

DR. T. E. SANDERS, St. Louis: Of the intraocular tumors, over 90 per cent are either the malignant melanoma of the uvea, a tumor of adults, or the retinoblastoma of infants. The problem of the intraorbital tumor is quite different. The exact nature of the tumor is not known until microscopic examination is made.

Lesions anterior to the orbital fascia are better considered to be in the lid. They present as superficial, palpable masses, without exophthalmos, and can be easily removed through a simple incision in the lid. The 17 dermoid cysts in this series would seem to be in this class. The author states that the majority of the 19 lipomas were situated anteriorly, presenting as a mass, and that the tumor was histologically indistinguishable from normal orbital fat. I believe that many of these lipomas were really a herniation of orbital fat through a small defect in the orbital septum, and were not neoplastic.

I agree with Dr. Forrest that the accurate diagnosis and classification of a tumor of the hematopoietic system is extremely difficult. Some of the lymphomas, better called lymphocytomas, are local tumors. However, the majority are associated with such systemic diseases as lymphosarcoma, leukemia and Hodgkin's disease, and thus should be considered a local manifestation of a general condition. The meningioma should also be considered a secondary tumor, as the majority of the 17 meningiomas in this series almost surely invaded the orbit from a lesion primarily intracranial.

I was interested in Dr. Forrest's group of mixed tumors of the lacrimal gland as it was exactly ten years ago, before this section (*Mixed Tumors of the Lacrimal Glands*, ARCH. OPHTH. 21:239 [Feb.] 1939; *Tr. Sect. Ophth., A. M. A.*, 1938, p. 214) that I reported a series of these cases. The present results again show that these tumors have an extremely high rate of recurrence, tend to be invasive and are potentially fatal. Therefore, I believe they cannot be considered benign.

It is not often that the opportunity arises to collect such a large and representative series of intraorbital tumors. The present series is particularly important, as adequate clinical data and the results of careful pathologic study are available. The data presented by Dr. Forrest are of value in several ways. His tabulation presents the types of tumors arising in the orbital tissues, with their relative frequency in this series. He has also correlated the variable clinical symptoms with the histologic picture. This knowledge will provide a much better idea of the pathologic possibilities in a particular case. The relatively large number of cases in this

*Retinoblastoma.*—One tumor was a retinoblastoma recurrent from an intraocular growth for which there had been enucleation eleven months prior to onset of swelling of the lid and appearance of the orbital mass. Cytologically, the tumor was identical with the usual intraocular neoplasm.

*Adenoma of the Pituitary Gland.*—The records indicated that a clinical diagnosis of suprasellar meningioma had been made in 1 case; the history was of fourteen years' duration. Microscopic examination of the specimen removed from the orbit revealed sheets of epithelial-like cells characteristic of the eosinophilic adenoma of the anterior lobe of the pituitary (fig. 17 D).

#### SUMMARY

A series of 222 cases of intraorbital tumor from the Registry of Ophthalmic Pathology were studied with particular attention to the histologic characteristics, but also with regard to clinical features. One hundred and eighty-four of the tumors were primary in the orbit; these included 93 of mesenchymal origin, 48 related to the nervous system, 25 mixed tumors of the lacrimal gland and 18 dermoids. Forty-four, or 24 per cent, of the primary tumors were malignant. Thirty-eight of the tumors examined were secondary in the orbit and included 24 carcinomas, 6 neuroblastomas, 6 malignant melanomas, 1 retinoblastoma and 1 adenoma.

Certain clinical features appeared to be characteristic of various classes of tumors. Lipomas and dermoids were often anteriorly situated in the orbit, while sarcomas, meningiomas, neurofibromas and gliomas were more frequently posterior and caused exophthalmos. Mixed tumors and hemangiomas were about equally divided between the two locations, approximately half of each causing exophthalmos.

Malignant mesodermal tumors, gliomas of the optic nerve, hemangiomas and metastatic neuroblastomas occurred predominantly in youth. The tumors of the hematopoietic system and secondary carcinomas were ordinarily concomitants of more advanced age. The age distributions of other types of tumor were less characteristic.

Among the histologically benign tumors, recurrence was most frequent in the mixed tumors and the hemangiomas because of the difficulty of removal; remnants of the tumor are often left behind and form the nucleus for continued growth.

In general, the data gathered from the 222 cases in this series are in agreement with those of other authors and support accepted views regarding treatment and prognosis in most categories.

# Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

## Comparative Ophthalmology

HEREDITARY APLASIA OF THE OPTIC NERVE IN THE MOUSE. HUGO J. BEIN, *Ophthalmologica* 113: 12 (Jan.) 1947.

Aplasia of the optic nerve was found in a number of animals in the "Basil waltzing mouse stock." The eyes were normal externally. This deformity was found to be hereditary and was frequently combined with a misshapen skeleton. It was found possible to continue to breed mice with optic aplasia.

F. H. ADLER.

## Cornea and Sclera

CEPHALOSPORIUM KERATITIS. A. J. BEDELL, *Am. J. Ophth.* 30: 997 (Aug.) 1947.

Bedell reports a case of corneal ulcer resulting from injury by a cow's tail. The clinical picture was so suggestive of a mold as the cause of the ulcer that potassium iodide was given, and satisfactory regression resulted. Subsequent investigation proved that the cause was the extremely rare *Cephalosporium* species.

W. S. REESE.

TREATMENT OF PERFORATED CORNEAL ULCER BY AUTOPLASTIC SCLERAL TRANSPLANTATION. S. LARSSON, *Brit. J. Ophth.* 32: 54 (Jan.) 1948.

In connection with an operation for retrobulbar hemangioma, a 7 year old girl had lagophthalmic corneal ulcer, which developed into a descemetocoele. Four attempts elsewhere to close the ulcer with a conjunctival flap did not lead to the desired result. The wound became larger, and there was danger of perforation. A scleral disk was punched out of the same eye and transplanted into the wound, after the edges of the latter had been excised. The graft was covered with conjunctiva. The result was good: The transplant fitted in comfortably, the ulcer closed, and vision was comparatively good.

W. ZENTMAYER.

THE SURGICAL TREATMENT OF PTERYGIUM. A. D'OMBRAIN, *Brit. J. Ophth.* 33: 65 (Feb.) 1948.

D'Ombrein considers that pinguecula and pterygium are fundamentally identical, etiologically and structurally, that the primary focus of activity is in the connective tissue and that efficient surgical treatment of pterygium must include removal of this tissue. After the pterygium is freed, its apex is grasped at its tip with fixation forceps and held up vertically and taut by an assistant. With fine forceps and sharp-pointed scissors, the whole subconjunctival portion of the pterygium, from the under surface of the epithelial layer as far medially as the plica semilunaris, is dissected off. This comes away in one triangular piece, and is a remarkably thick and extensive structure underlying the whole extent of the pterygium; indeed, it is the pterygium. A sliver of the

series in which final clinical results were known gives a clearer understanding of the prognosis of these tumors.

The orbital tumors remain a real clinical problem. Although the symptoms are usually characteristic, the diagnosis of the presence of a tumor in the orbit is at times difficult. In my experience, roentgenograms often do not show bony defects in the orbit, and, thus invasive tumors are not recognized as such before operation.

DR. ALAN C. WOODS, Baltimore: How does Dr. Forrest classify the ordinary pseudotumor, by whatever name he chooses to call it? Dr. Walter Dandy found that about 20 per cent of his large series of tumors were lesions of Christian-Schüller disease. I was rather surprised at the absence of this entity in the present series.

DR. ARNOLD W. FORREST, New York: There can be no doubt as to the anatomic anterior limit of the orbit, but, as pathologists, we were all, of course, entirely dependent on the clinicians' description of where the tumors lay. The question whether the lipomas were true tumors or herniations had to be considered, but we could do no more than accept the clinicians' word for the fact that the tumors lay within the orbit.

The question of the lymphoma is an extremely interesting one. Dr. Sanders comments that it should be considered part of the generalized disease rather than as an isolated lesion. Schulz and Heath (*Radiology* 50:500-505 [April] 1948) pointed out that the lymphoma of the orbit is more commonly an isolated lesion and does not carry the grave implications of lymphomas elsewhere. I believe that the experience of Dr. Hayes Martin, at Memorial Hospital in New York, substantiates the statement that lymphomas in the head and neck in general are different from lymphomas elsewhere and do not carry the grave prognosis of such lesions. We did follow the patients; and, although 2 showed evidence of leukemia and 2 others signs of generalized disease within a year, 4 or 5 of them were well after as long as five and ten years. Meningioma, often a primary tumor, might in other cases be secondary to meningioma within the skull.

Dr. Woods's observation that cases of pseudocellular tumors and of Christian-Schüller disease are absent from this series is a valid remark from the clinical point of view, but from the standpoint of the pathologist it seemed wise to exclude them as representing inflammation rather than neoplasm.

panophthalmitis, with partial or complete loss of vision, have been frequent. These severe complications of the eyes did not occur in 9 patients treated by the authors with sulfonamide compounds and/or penicillin. Five patients were treated with sulfonamide drugs and 4 patients with penicillin systemically or topically or both. Complete recovery without sequelae occurred in all but 1 patient, who had mild conjunctivitis with slight symblepharon, but no corneal involvement. Enthusiasm for any type of therapy in this syndrome must be tempered by recognition of the fact that the severity of the clinical course varies greatly and that recovery without ocular complications is not uncommon. In 6 of the 9 cases at least one previous attack was experienced without permanent ocular damage.

W. ZENTMAYER.

### General Diseases

CORNEAL LESIONS IN HODGKIN'S DISEASE. P. MATTEUCCI, *Am. J. Ophth.* 30: 136 (Feb.) 1947.

Matteucci reports a case of Hodgkin's disease in which a bilateral herpetic type of keratitis appeared. He notes the rarity of this complication, the effect of radium therapy on the ocular condition, confirming the sensitivity of specific cells of malignant lymphogranuloma to radium, and the probable etiologic association between the supposed virus of lymphogranuloma and the corneal lesions.

W. S. REESE.

OCULAR MANIFESTATIONS OF MUMPS. J. FIELDS, *Am. J. Ophth.* 30: 591 (May) 1947.

Fields reports a case of keratitis due to mumps; he describes the condition as a definite clinical entity and suggests the term "mumps keratitis."

W. S. REESE.

OCULAR CHANGES IN ACUTE DISSEMINATED LUPUS ERYTHEMATOSUS. F. C. CORDES and S. D. AIKEN, *Am. J. Ophth.* 30: 1541 (Dec.) 1947.

Cordes and Aiken report a case of acute disseminated lupus erythematosus with autopsy. They conclude from the study of this case and a review of the literature that there is no pathognomonic ocular lesion or combination of lesions in this disease, but that the so-called toxic retinitis is probably the most typical and frequent pathologic change.

W. S. REESE.

OCULAR EXPRESSIONS OF DIABETES. I. GIVNER, *New York Med.* 3: 5 (March 5) 1947.

Givner reviews the literature on ocular manifestations of diabetes. A survey of 127 patients with juvenile diabetes showed 3 patients, aged 12, 15 and 15, who had had diabetes eight, eleven and nine years, respectively. Each showed pinpoint hemorrhages and venous dilatations, with no arterial changes. In no case were exudates seen which suggested that hemorrhages precede the appearance of the waxy exudate.

A rare observation was made on a patient with phlebosclerosis associated with diabetes of seventeen years' duration in that the aqueous vein showed phlebosclerosis.

W. ZENTMAYER.



free edge of the remaining conjunctiva is excised, leaving a bare strip of sclera several millimeters in width. The conjunctiva rapidly grows over the scleral strip, but not before the corneal surface has healed.

W. ZENTMAYER.

### Experimental Pathology

SOME RESEARCHES ON THE RESPIRATION OF THE CORNEA IN ALBINO RATS. A. BAKKER, *Brit. J. Ophth.* 31: 100 (Feb.) 1947.

Bakker gives the following summary of experiments which had as their object the study of the influence of various concentrations of carbon dioxide and the absence of oxygen in the surrounding atmosphere on the cornea of anesthetized albino rats. With the help of artificial breathing, it was possible to close up the animals in a tank filled with one kind of gas or another, and in this way to expose the eyes of the experimental animals under otherwise normal conditions to the gas under investigation. As a result of these experiments, Bakker is of the opinion that carbon dioxide is able to penetrate through the cornea from the surrounding atmosphere to the anterior chamber. It could be determined that the so-called selective penetration of carbon dioxide through the cornea is not probable. Absence of oxygen in the surrounding atmosphere does not inhibit the normal life of the cornea. The corneas remained transparent for many hours in an atmosphere of 8 per cent carbon dioxide and 92 per cent nitrogen. Special attention was paid to possible pathologic changes in the corneas after the experiments were concluded.

The article is illustrated.

W. ZENTMAYER.

EXPERIMENTAL HYPERTENSIVE RETINOPATHY. N. BELMONTE GONZALEZ, *Arch. Soc. oftal. hispano-am.* 7: 214 (March) 1947.

The author, having made observations on the fundus oculi in dogs subjected to experimental hypertension, came to the following conclusions: 1. Experimental nephrogenic chronic arterial hypertension in the dog in the end produces changes in the fundus similar to those occurring in man with hypertensive vascular sclerosis. 2. The retention metabolites brought about by total renal insufficiency after bilateral nephrectomy do not give rise to any retinal changes, for the same reason that they do not produce an increase in arterial tension. 3. Ligation of both ureters in the dog creates pathophysiologic conditions in the ocular fundus which bring about angiospastic retinitis.

The article is illustrated.

H. F. CARRASQUILLO.

### General

STEVENS-JOHNSON SYNDROME. D. O. WRIGHT, E. M. GOLD and G. JENNINGS, *Arch. Int. Med.* 79: 510 (May) 1947.

Wright and his associates point out that the syndrome described by Stevens and Johnson in 1922 was designated as a "new" eruptive fever associated with stomatitis, ophthalmia, cutaneous eruption and constitutional symptoms. The syndrome deserves emphasis because tragic complication involving the eyes, consisting of corneal ulceration or

90 C.; this is then maintained for the remaining ten seconds. The eye is not patched after operation.

After the operation, there is moderate chemosis, which lasts for eight to ten days. There is hypesthesia of the cornea, which may be accompanied with roughening of the epithelium. This disappears rapidly. The authors have never seen a case of iritis following the operation. Occasionally, there may be slight mydriasis. There may be a tendency to myopia for a few days. This is ascribed to edema of the ciliary body affecting the zonule of Zinn. There is some edema of the retina in the extreme periphery. This gradually subsides, and one is left with scars, as seen after an operation for disinsertion. They are not enough to interfere with the visual field.

The authors have performed thirty-five operations according to the technic described. The results have equaled those of the perforating cyclodiathermy, and fewer complications have been encountered. They think that cases of chronic glaucoma are the most satisfactory for this type of operation.

The paper concludes with the authors' theory as to the physiologic basis for the operative results.

P. R. McDONALD.

APPRECIATION AND MECHANISM OF THE DESTRUCTIVE EFFECTS PRODUCED BY OCULAR HYPERTENSION. AMADEO NATALE, *Arch. d'opht.* 7: 129, 1947.

The author reviews the more recent literature, chiefly the English and American, which has to do with glaucoma. He calls attention to the two types of tension: (1) the dynamic, due to the contents of the sclera, and (2) the static, due to the rigidity of the scleracorneal coat. He discusses intraocular pressure in relation to the cerebrospinal fluid pressure. He refers briefly to the control of the hydrostatic pressure within the eye. He also goes into detail in regard to the pupillary reactions. The close association between the blood and the aqueous humor is taken into consideration. The author points out that he has not tried to make use of all the immense bibliography which he has accumulated. An extensive bibliography is appended.

S. B. MARLOW.

INCOMPLETE GLAUCOMA. ROBERT GERARD, *Arch. d'opht.* 7: 511, 1947.

The author presents 5 cases of incomplete glaucoma with studies of the visual fields. He discusses the cupping of the disk, the field defects, the pupillary changes and the changes in the arterial tension of the retina. He concludes that the idea of an incomplete glaucoma is justified. Glaucoma without hypertension is one of the most typical forms of the disease. The pupillary changes, the field defects and the cupping observed without hypertension are characteristic and are to be differentiated from primary atrophy of the optic nerve. He expresses the belief that the cupping in this form of glaucoma is not due to compression of the nerve by intracranial vascular sclerosis.

S. B. MARLOW.

THE EFFECTIVENESS OF A MODIFIED CYCLODIALYSIS. LADISLAUS GAT, *Ophthalmologica* 114: 106 (Aug.) 1947.

The author believes that with the Blaskovics-Kettesy modification of cycloidalysis glaucoma can be cured in most cases. The advantages of

XANTHELASMA. AND AUTONOMIC NERVOUS SYSTEM: A NEW SYNDROME. A. BAKKER, Brit. J. Ophth. 31: 686 (Nov.) 1947.

Bakker gives the following summary: Almost without exception, patients with xanthelasmas have various kinds of allergic disease; and, if they do not, allergic disorders occur, at any rate, among their relatives. As these benign tumors are probably closely related to the cholesterol metabolism and the latter stands under the regulating influence of the autonomic nervous system, and as, in the last analysis, allergic disorders have much to do with the sympathetic and the parasympathetic nerves, an attempt is made to consider all these apparently heterogeneous diseases from one viewpoint, i. e., as a dysfunction of the vegetative nervous system.

W. ZENTMAYER.

### Glaucoma

TECHNIC OF NONPERFORATING CYCLODIATHERMY. L. WEEKERS and R. WEEKERS, Ann. d'ocul. 180: 76 (Feb.) 1947.

In a previous article the authors reviewed the history of this operation. They believe that the effect of the diathermy is to produce an intense vasodilatation of the uveal tract. This is brought about by action on the ciliary nerves, as well as a "biochemical" lesion in the uvea.

They do not think that it is necessary to perforate the sclera in order to obtain the desired effect of lowering the tension. On the basis of their experimental work and their results with patients, they conclude that the most satisfactory position in which to place the electrode is 7 to 8 mm. from the limbus, in the region of the ora serrata. One then gets the maximum vasodilatation, and there is less risk of injuring the lens. They also feel that when this operation is performed the entire ciliary body should be treated. Originally they made eight applications of the diathermy; now they use approximately twenty applications, with a weaker current. The authors feel that the effect of the cyclodiathermy is somewhat analogous to that of multiple cyclo-dialyses.

The electrode should have a diameter of about 0.75 mm. If one uses a small electrode, the lesion in the ciliary body is more discrete; and since the conjunctiva is not dissected from the globe, there is less conjunctival reaction. The authors employ a pyrometric electrode, which permits an accurate gage of the temperature.

The instrument is described fully. There are two fine wires, one of which carries the current and acts as the first element of the thermocouple. The second wire is the other element of the thermocouple. Each instrument is calibrated before use.

For operation the eye is prepared in the usual manner. Local anesthesia consists of topical application of cocaine and epinephrine, as well as retrobulbar injection. Just prior to operation retrobulbar injection of 1 cc. of 40 per cent ethyl alcohol is given. This is to augment the effect of the anesthetic and to prevent the rise in tension that may occur immediately after the operation. The electrode is applied through the conjunctiva about 8 mm. from the limbus, in the region of the ora serrata. This is so that the nerves to the ciliary body will be affected. The number of applications varies from twelve to twenty. The electrode is held in place for fifteen seconds. The current is raised so that within five seconds the temperature registers

the literature in human cases, occurred often in the animals. It is uncertain whether the reaction is specific for aluminium.

Among other oddities were noted bullous keratitis, 2 cases; staphyloma (false buphthalmos), 1 case; zonular keratitis, 2 cases; interstitial keratitis, 1 case; deep keratitis, 1 case; pigmented cornea, 2 cases; pigmented limbus, 1 case, and folds in Descemet's membrane, 2 cases.

Histologic investigations were hampered by technical difficulties. The changes observed were such as would have been expected from the clinical findings. They included hyalinization and vascularization of the cornea, iritis, atrophy of the iris and abnormal pigmentation of the iris. Pathologic changes in the retina and choroid were noted in many instances. Abortive attempts were made to trace the distribution of the aluminium through the tissues by staining reagents. On the clinical and experimental evidence, it is concluded that the eye is by no means inert to aluminium.

In an appendix, protocols of the experimental study are summarized, and the report on the histologic specimens is fully illustrated. The article contains nineteen illustrations, including several colored plates.

W. ZENTMAYER.

#### INDIRECT GUNSHOT INJURY OF THE EYE SIMULATING ELLIOT'S TREPHINING OPERATION. A. LOTIN, *Vestnik oftal.* 26: 70, 1947.

A private aged 20 gave a history of having been injured in the left eye three years previously. A smooth linear scar, 3 cm. long, was visible at the left upper lid, at the inner orbital wall near the brow. It was not adherent to the orbital bone. The left eye presented a classic, oval trephine opening, at the limbus at 12 o'clock, with a filtering scar and a complete small coloboma of the iris. The fundus was normal, and vision was corrected to 0.9. At the hospital where he was treated after the injury no operative intervention was recorded. Evidently, the bullet caused the perforation of the sclera and injury of the iris, simulating a perfect Elliot trephination with iridectomy.

O. SITCHEVSKA.

#### Methods of Examination

#### APPEARANCE OF THE NORMAL FUNDUS AS STUDIED BY STEREO-OPHTHALMOSCOPY. ARCHIMEDE BUSACCA, *Arch. d'opht.* 7: 361, 1947.

By means of the Goldmann slip lamp and with a contact glass modified by the author, stereoscopic examination of the fundus of the eye is possible; for this reason, the author uses the term stereo-ophthalmoscopy. He describes four different planes of the retina which can be identified by this method of examination. The first is the plane corresponding to the internal limiting membrane of the retina. The plane between the retina and the choroid has three aspects: the retinal pigmentary, the anterior choroidal and the specular plane. These three planes are difficult to separate. The third plane is the plane of the large choroidal vessels, and the fourth is that of the sclera. These planes, of course, are identified with the use of a narrow slit. The author believes that by this method a much more careful study of the fovea centralis and the macular region is possible. The method allows better correlation of the facts known concerning the vessels, their confirmation and structure, and the

the method are the ease of procedure, its adaptability to all forms of glaucoma, the possibility of repetition on the same eye and absence of bad effects when the operation is a failure. The disadvantages are that the intraocular tension is lowered only on the third to fourth day after operation and that there is always the possibility of some bleeding. The author has also noted a postoperative myopia which he believes stops spontaneously after several months. The clinic in which the author works has used this method successfully in 74.5 per cent of cases of glaucoma.

F. H. ADLER.

### Injuries

THE EFFECT OF ALUMINIUM AND ITS ALLOYS ON THE EYE. L. H. SAVIN, *Brit. J. Ophth.*31:449 (Aug.) 1947.

This voluminous report was presented to the Vision Committee of the Medical Research Council. The subject is considered under the following headings: introduction; clinical report of cases of intraocular fragments of the aluminium; alloys; experimental observations on rabbits; illustrative experiments, and histologic changes. The author summarizes as follows:

The literature of intraocular aluminium is reviewed. A case is reported in which a piece of "aluminium zinc" (or possibly zinc base aluminium) was observed over a period of three years as it lay on the retina of an only eye. The metal was at first bright and silvery. Later it became coated with a white cover, probably of aluminium hydroxide. The fragment shifted twice, each time leaving a retinal "imprint," before eventually disintegrating into white powder. In a second case the behavior was similar.

Twenty-five implantations of fragments of aluminium or aluminium alloy were made into the anterior chambers of rabbits by a standardized technic, and 9 implantations were made into the vitreous chamber. There was no clinical difference in the behavior of pure aluminium and that of the various alloys. Doses varying from 0.3 to 20 mg. were used; the ocular reaction tended to be severer with the higher doses.

The fragments were observed to become coated with white powder, with yellowish exudate, with fibrin or, in late cases, with jelly. A late change often seen was powdering and fragmentation of the metallic fragment. In 6 cases the fragment was completely absorbed. Common local changes were necrotic "imprints" left by the metal; of these, 6 imprints were on the cornea, 12 on the iris (9 gray, 2 white, 1 necrotic), 2 in the lens and 4 in the fundus.

Of the general ocular effects on the eye were lenticular opacities, including striae, dots, vacuoles and irregular opacities, in 28 eyes; these opacities were occasionally accompanied with polychromatic luster. The opacities were anterior capsular in 5 eyes, anterior cortical in 6 eyes, posterior cortical in 4 eyes, capsular imprints in 2 eyes and complete cataracts in 3 eyes.

Quiet inflammatory changes in the uveal tract were frequent. These included posterior synechias, 10 cases; iris bombé, 2 cases, and atrophy of the iris, 14 cases. Other changes included pathologic pigmentation of the fundus, in 23 cases; localized choroiditis, in 6 cases, and retinitis proliferans, in 3 cases. Pathologic vascularization, not reported in

extremely frequent. Optic neuritis leading to atrophy of the optic nerve may be present. These ocular symptoms, though benign, are important as expressions of a highly localized and dangerous form of poliomyelitis.

ARNOLD KNAPP.

PATHOGENESIS AND PATHOPHYSIOLOGY OF COAL MINER'S NYSTAGMUS.  
M. PECHDO and L.-L. GAYRAL, Arch. d'opht. 7: 521, 1947.

The authors review the work which has been done on this condition and discuss the various hypotheses which have been proposed to explain it. They express the belief that pendular nystagmus in coal miners is due to an intoxication of the nerve centers by methane (firedamp) and that the site of the lesion is in the neighborhood of the nuclei and pathways of the mesencephalon concerned with nystagmus. More particularly, they believe that this nystagmus may well correspond to the system which controls reflex fixation and fusion. Nystagmus is a symptomatic expression of lesions of these pathways or centers. Finally, they assert that there is no reason to preserve the mechanical theory of fatigue or of amblyopia arising from insufficient light. They have no explanation as to why nystagmus develops in some miners and not in others. They refer to the compensation aspect of the problem as it exists in Belgium and France, as compared with other countries.

S. B. MARLOW.

### Operations

THE USE OF THE MASSETER, TEMPORALIS AND FRONTALIS MUSCLES  
IN THE CORRECTION OF FACIAL PARALYSIS. W. MILTON ADAMS,  
Plastic & Reconstruct. Surg. 1: 216, 1946.

Of the methods used to correct the defects of facial paralysis, the best is nerve grafting. Unfortunately, this can be done in only a limited number of cases. The next best method is muscle substitution. This permits some motion without the associated distortion that nerve substitution produces. Fascial strips give a better primary result, but no motion is obtained and sagging is apt to recur.

For the closure of the eyelids, a strip of the temporalis muscle is transplanted into the margin of the upper and lower lids. While not perfect, this procedure is worth while. Motion to a paralyzed brow is obtained by transplanting a band from the active fellow frontalis muscle.

L. P. GUY.

RECENT ADVANCES IN OPHTHALMIC SURGERY. ALSTON CALLAHAN,  
South. Surgeon 13: 92 (Feb.) 1947.

The author discusses corneal transplantation, unilateral aphakia and scleral resection. Some of the newer technics and instruments used in corneal transplantation are shown by illustration. The technic of using a contact lens on the aphakic eye to overcome diplopia is described. A drawing of the operative technic of a scleral resection is shown, with a short review of the recent papers on this subject.

C. P. GRANT.

NYLON THREAD IN OCULAR SURGERY. P. HALBRON and H. AITOFF,  
Bull. Soc. d'opht. de Paris, November-December 1946, p. 30.

Halbron and Aitoff have found that nylon sutures are most resistant to traction, easily manipulated, have a smooth surface, cause no swelling.

relation of the planes and layers described in the different portions of the eye. With the use of his modification of the contact lens, he finds it possible to examine any part of the fundus. The subject is presented in some detail.

S. B. MARLOW.

QUALITATIVE AND QUANTITATIVE PERIMETRY WITH MONOCHROMATIC TARGETS AND WITH WHITE TARGETS OF THE SAME LUMINOUS INTENSITY. P. MATTEUCCI, *Rassegna ital. d'ottal.* 13: 36, 1946.

The author studied fields of vision using monochromatic targets of equal subjective brilliance, as determined for each subject by means of flicker photometry. Perimetric examination was performed after adaptation to darkness, or after adaptation to a gray surface having an illumination equal to the gray surface of the perimeter. Behavior of the limits of the field for color was variable, and the limits were different even when monochromatic targets of the same size and brilliance were used. In quantitative perimetry the eye shows greater sensitivity to differences in contrast than to variation in size of test objects used. The results the author obtained differ greatly from those obtained by previous investigators, who used, under similar experimental conditions, spectral targets more or less monochromatic having equal energy content or luminosities. From these variations in the retinal sensitivity for the same color and the existence of factors not easily controllable, it is hard to define the limits of the visual field for colors, even if an average spectral visibility curve for peripheral vision is adopted. He expresses doubt as to the accuracy and value of employing colors in clinical perimetry.

G. B. BIETTI—J. J. LoPRESTI.

Neurology

OCULAR SYMPTOMS OF POLIOMYELITIS. Annotation, *Brit. M. J.* 2: 620 (Oct. 18) 1947.

Kindt and Knudtson (*Acta ophth.* 24: 295, 1946) report on an epidemic of poliomyelitis in which 279 patients were affected: Thirty-seven patients showed bulbopontile lesions, 23 of whom had ocular symptoms; of these, 5 were under the age of 15 and 3 of them died; of the 18 adults, 2 died. Diplopia was the first symptom in 3 patients. In the other patients the ocular symptoms came on between four and eleven days after the onset. In 20 of the 23 patients the diplopia was combined with blurred vision. The diplopia was constant in some and transient in others. Nystagmus was present in 6 patients and unilateral ptosis in 1 patient. Paresis of the third nerve was observed in 3 patients. Paresis of the ocular muscles was regarded as nuclear in origin, and paralysis of the associated ocular movements, observed in 5 patients, as supranuclear in type.

The authors conclude that the frequency of ocular symptoms varies in different epidemics. Paresis of the sixth nerve, usually unilateral and transient, is the most frequent; paresis of the third nerve, rarely total and in most cases occurring with ptosis, with or without some degree of ophthalmoplegia, is next. Paresis of accommodation was noted in other epidemics. Trochlear paresis was recorded only once in the literature. Nystagmus, in conjunction with paresis of the ocular muscles, was

SOFTENING OF THE RETINA IN SECTORS AND DETACHMENT. PIERRE DOUCET, Arch. d'opht. 7: 167, 1947.

Two cases are reported in which only the area supplied by an artery was affected. A triangular lesion resulted, at the apex of which there were arteritis and disturbance of the return circulation, and, farther out, thinning of the retina with lenticular plaques, appearing like peas on a veil. The base of the triangle was represented by fine, floating threads, the last vestiges of the membrane. At the equator occurred a retinal tissue, which differed in the 2 cases. In 1 case there was atrophy with pigmentation; in the other the retina appeared healthy. The author calls attention to the triangular shape of the lesion as a possible explanation for the production of detachment and tears as the result of disease of an artery.

S. B. MARLOW.

APPARENT BLINDNESS OF THE NEWBORN—GRAY PSEUDOATROPHY OF THE OPTIC NERVE. BEAUVIEUX, Arch. d'opht. 7: 241, 1947.

The author first describes the case of an infant 4 months of age at the time of first examination, twenty-three years before, when he had given a poor prognosis because of the presence of dilated pupils and a grayish, atrophic appearance of both optic nerves. Nine months later the pupils reacted definitely to light, but the ophthalmoscopic appearance was unchanged. Still later, some vision was reported, as manifested by the child's attempt to grasp objects; and later still, visual acuity was reported to accord with the refractive error and nystagmus. Since the observation of this case, the author has seen 8 similar ones. He gives a brief review of the literature. He expresses the opinion that the condition should be known to all ophthalmologists in order that they may avoid the diagnostic error which he himself had made. Cases of this condition may be divided into two groups: (1) cases in which a satisfactory and rapid recovery of vision takes place, and a change in the ophthalmoscopic picture occurs, and (2) cases in which visual development is less satisfactory and a number of sequelae occur, such as chorioretinal pigmentation, posterior polar cataract, strabismus, nystagmus and high myopia. He discusses the atrophy from the point of view of syphilis, tuberculosis and alcoholism and of the action of a neurotropic virus. He points out that there are plausible arguments in favor of a delayed myelination of the optic pathways. He presents this evidence and discusses the role that is played by myelin in the transmission of the light stimulus. Two color plates illustrate the cases.

S. B. MARLOW.

SURGICAL CURE OF DETACHMENT OF THE RETINA WITH PERFORATION OF THE MACULA: REPORT OF A CASE. DOUCET, Arch. d'opht. 7: 284, 1947.

In a case of high myopia, the author was able to reach the region of the tear by dividing the external rectus muscle. A successful result was obtained, with some improvement in vision. The author points out that there are two technical difficulties in the operation and expresses the belief that some procedure should be developed which will not completely destroy the macula and result in severe loss of vision.

S. B. MARLOW.



in tissue and produce no inflammatory reaction. Sterilization is easy by the usual methods, without loss of their properties. The authors have used the sutures clinically in fixation through the superior rectus muscle in cataract extraction, in the sewing of the flap in operations for glaucoma, in muscle surgery, in evisceration when a prosthesis is sewed into Tenon's capsule, for muscle retention suture in detachment operation and in all plastic operations about the eye. The nylon suture is readily removed.

L. L. MAYER.

### Orbit, Eyeball and Accessory Sinuses

EXOPHTHALMOS WITH INTERMITTENT AGGRAVATION: A SPECIAL FORM OF VARIABLE EXOPHTHALMOS. RAFFAEL CAMPOS, Arch. d'opht. 7: 390, 1947.

The author reports the case of a girl aged 16 who had been affected since childhood with exophthalmos of the left eye, which was increased passively by tilting the head forward and on crying and effort. A roentgenogram revealed round opacities, resembling phleboliths, in the upper outer portion of the orbit. Although the exophthalmos disappeared after one operation, it recurred at the end of a year. The second surgical approach, by means of the Krönlein technic, revealed saccular dilatations of the orbital veins. The exophthalmos was cured, and visual acuity, which had decreased to 2/10 before operation, rose to 5/10. In discussing the various forms of variable exophthalmos, the author suggests a new and more exact classification. He defines as exophthalmos with intermittent aggravation the type described here and insists that this form of exophthalmos may be produced not only by an angioma of the orbit but also by varicosity of the orbital veins.

S. B. MARLOW.

### Pharmacology

VISUAL EFFECTS OF TRIDIONE. L. L. SLOAN and A. P. GILGER, Am. J. Ophth. 30: 1387 (Nov.) 1947.

Sloan and Gilger found that after treatment with trimethadione ("tridione"; 3,5,5-trimethyloxazolidine-2-4 dione) acuity, brightness sensitivity, color discrimination and sensitivity to flicker showed temporary impairment when both the foveal field and a surrounding area of 6 to 10 degrees were illuminated to a high brightness. With continued exposure to the high brightness visual function improved, and tolerance to the visual side-effects developed with continued medication.

W. S. REESE.

### Retina and Optic Nerve

CAPILLARY FRAGILITY AND CAPILLARY PERMEABILITY IN RELATION TO RETINAL HEMORRHAGES. R. L. SHANNO, J. O. GRIFFITH JR. and W. O. LAMOTTE JR., Am. J. Ophth. 30: 1556 (Dec.) 1947.

Shanno, Griffith and LaMotte conclude from their studies that routine is probably of value in preventing further retinal hemorrhages in patients in whom the initial hemorrhage was associated with a generalized capillary fault.

W. S. REESE.

## Correspondence

### MUSCLE SCHEMAS

*To the Editor.*—Dr. Adler's review of Dr. Epstein's book on "Strabismus" (ARCH. OPHTH. 39:840 [June] 1948), touches on a point that merits some discussion. Dr. Adler points out some errors, e. g., illustration 5 and statements on page 9 bearing on ocular torsion. Both these errors can be traced to the illustrations and legends no. 581 and 582 in Duke-Elder's "Text-Book of Ophthalmology" (London, Henry Kimpton, 1932, vol. 1, p. 595). Dr. Epstein simply took the illustrations and legends uncritically and used them in his book.

This uncritical repetition of wrong and misleading diagrams in book after book is unfortunate. A diagram on muscle action in Hansell and Reber's "Ocular Muscles," second edition (Philadelphia, P. Blakiston's Son & Co., 1912, p. 28) leads the authors to say that "in movement of the eyes up and to the right, the two muscles principally concerned are the right inferior oblique and the left superior rectus; down and to the left, the right inferior rectus and the left superior oblique, and so on . . ."

This misleading diagram and the incorrect statement, which must also have appeared in the earlier first edition, have been copied since in numerous textbooks. This diagram, with the confusing notation, is also found in Peter's "Extra-Ocular Muscles," third edition (Philadelphia, Lea & Febiger, 1941, p. 62, fig. 33), and even in so carefully written a book as Spaeth's "Principles and Practice of Ophthalmic Surgery," fourth edition (Philadelphia, Lea & Febiger, 1948, p. 210, fig. 155). It is also repeated, together with the incorrect statements, in Duke-Elder's "Text-Book of Ophthalmology," volume 1, pages 611 and 612. When Duke-Elder does not use this confusing muscle schema, he gives the action of the aforementioned muscles correctly, viz., in his "Practice of Refraction," third edition (Philadelphia, P. Blakiston's Son & Co., 1938, p. 198).

Some books do not use any muscle schema, possibly because of this tendency to confusion. However, this is not an unmixed blessing, as it makes the subject much more difficult for the student, and sometimes even catches the author off guard. Thus, in Berens and Zuckerman's "Diagnostic Examination of the Eye," (Philadelphia, J. B. Lippincott Company, 1946, p. 191), is the statement that "there is extorsion in looking upward and inward, or in looking downward and outward; and there is intorsion in looking upward and outward or downward and inward."

It was in an effort to eliminate the recurrent source of confusion from the aforementioned diagram that I searched for a simpler and safer muscle schema, one that would be all embracing and yet be easily remembered. This resulted in the development of the benzene ring muscle schema, with its fifteen diagnostic features.

JOSEPH I. PASCAL, M.D., New York.

37 West Ninety-Seventh Street (25).



and perimetry is given. This four year program leads to the degree of Bachelor of Science and the diploma in orthoptics. Miss Ann Stromberg is technical director of the practical aspects of the work at the hospital.

#### SOCIETY NEWS

**The Ophthalmological Society of Australia (British Medical Association).**—The eighth annual general and scientific meeting of the Ophthalmological Society of Australia (British Medical Association) was held at the University of Western Australia, Perth, commencing on Aug. 16, 1948 and continuing for the week. The scientific meeting was held in conjunction with the Section on Ophthalmology of the Australasian Medical Congress, Sixth Session, and the president of the section, Dr. J. Bruce Hamilton, occupied the chair. The principal guest was Prof. Frank B. Walsh, of the Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine.

The president of the Ophthalmological Society of Australia (British Medical Association), Claude Morlet, M.B., was precluded by illness from presiding at the annual general meeting of the society, and the chair was occupied in this case by the immediate past president. Members present included 5 from New South Wales, 5 from Victoria, 1 from Tasmania, 5 from South Australia and 8 from Western Australia.

Dr. Arthur H. Joyce was elected president of the society for the ensuing year, and Dr. E. J. McGuinness, vice president.

It is proposed to hold the ninth annual general meeting at Melbourne in the first week of October 1949, and the tenth annual general meeting at Brisbane in June 1950, in conjunction with the Australasian Medical Congress, Seventh Session.

**Southern Section, Association for Research in Ophthalmology Organized.**—On October 26, during the meeting of the Southern Medical Association in Miami, Fla., the Southern Section of the Association for Research in Ophthalmology was organized. Dr. Conrad Berens gave a brief résumé of the development and achievements of the national association. Dr. George Haik presented further work on beta irradiation for glaucoma. Dr. Alston Callahan was asked to serve as chairman of the Southern Section for the coming year. The following ophthalmologists attended: Drs. Conrad Berens, Shaler Richardson, George Haik, William Sayad, Don Boles, W. R. Johnson, William Hester, Karl Benkwith, Samuel McPherson, Carl Dunaway, Stacy Howell, Curtis Benton Jr., Hugh Parsons, E. R. Veirs, Frank Costenbader, Mason Baird, Philip Lewis and Alston Callahan.

**Eastern Section of Association for Research in Ophthalmology.**—The first meeting of the Eastern Section of the Association for Research in Ophthalmology was held Saturday afternoon, November 13, at Lenox Hill Hospital, New York. The 184 members and guests registered heard the following scientific program: "Ocular Changes Associated with Scrub Typhus," Dr. Harold G. Scheie and Dr. Wilfred E. Fry, Philadelphia; "Some Biologic Problems in Vision," Dr. Samuel Detwiler, New York; "Recent Concepts in Aqueous Humor

# News and Notes

EDITED BY DR. W. L. BENEDICT

## GENERAL NEWS

**The American Board of Ophthalmology.**—The American Board of Ophthalmology wishes to make known that it does not evaluate, approve or disapprove any ophthalmic residency with respect to its filling the requirements for candidates for board examinations. Any candidate who qualifies for the board examination and completes the prerequisites as outlined in the syllabus will be accepted. A copy of the syllabus can be obtained from the secretary of the American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

## UNIVERSITY NEWS

**Annual Postgraduate Ophthalmologic Conference, Department of Postgraduate Medicine of the University of Michigan.**—The department of ophthalmology of the University of Michigan Medical School will give its annual postgraduate conference from March 7 to 9, inclusive, 1949. The conference offers a review of fundamental principles through lectures, demonstrations and operative procedures by physicians of national prominence, as well as an opportunity to observe the application of modern developments in ophthalmology.

It is not designed to prepare practitioners for specialization; rather, its purpose is to give those who are now prepared to practice ophthalmology a new point of view and a new impetus for further study and investigation, as well as to offer to all in attendance the benefit of the experience of others in the subjects covered.

The fee for the course is \$25, payable on application.

Ophthalmologists are to bring their ophthalmoscope, since one-half day will be devoted to clinical demonstration of numerous interesting conditions of the fundus related to general disease.

Rooms have been reserved at the Michigan Union, Ann Arbor, for physicians enrolled in this conference. If reservation is desired, request should be sent directly to the room clerk as soon as possible, as a limited number of beds have been allotted for this conference.

Detailed programs may be obtained from Howard H. Cummings, M.D., chairman, department of postgraduate medicine, University Hospital, Ann Arbor, Mich.

**School of Orthoptics, Massachusetts Eye and Ear Infirmary.**—A school of orthoptics has been started at the Massachusetts Eye and Ear Infirmary, in conjunction with Simmons College, in Boston. During the first three years students at the college take courses that will give them an adequate scientific background. Their fourth year is spent at the hospital, where practical and didactic work in orthoptics

## Book Reviews

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**Principles and Practice of Ophthalmic Surgery.** By Edmund B. Spaeth, M.D. Fourth edition. Price, \$15. Pp. 1,049, with 649 illustrations, containing 1,251 figures and 8 colored plates. Philadelphia: Lea & Febiger, 1948.

This standard textbook has been thoroughly revised to include all the recent advances in its field. The numerous additions to the text are largely in the form of liberal quotations from various sources. While the value of the volume as a reference work is greatly enhanced by them, the reviewer found it difficult at times to determine the author's own personal views. The chapter on pathology of the orbit has been greatly enlarged to include a full discussion on the medical, as well as the surgical, treatment of thyrotoxic and thyrotrophic exophthalmos. In decompression of the orbit in extreme cases of malignant exophthalmos, the author favors removal of its lateral wall rather than its roof. A rather full description of some of the more recent technics for integrated implants is given in the chapter on enucleation. The physiology of strabismus and its nonsurgical treatment are ably presented, and much new material has been added in the discussion on the surgical aspects of this subject. The author's great interest in plastic surgery is evidenced by the completeness with which this part of ophthalmic surgery is covered. The same is true of blepharoptosis, to which 65 pages are devoted. These chapters more truly represent the author's own personal views than do most of the others and constitute the most important part of the book. The subject of retinal separation is well discussed and in sufficient detail. The chapters on keratoplasty, radium therapy and goniotomy are only amplifications of opinions expressed by the contributing authors.

The great popularity of this book is amply deserved, and in each edition every effort has been made to eliminate the faults of its predecessor. This current volume represents the fourth rewriting, and it is well done. A few misspellings and typographic errors still exist to detract from an otherwise excellent work.

The book gives the ophthalmologist the current views on all surgical subjects in a clear and concise manner. The author is to be congratulated for again having brought forth a textbook of which he can be justly proud. It has had, and will continue to have, a prominent place in every ophthalmologist's library.

JOHN H. DUNNINGTON.

**Documenta Ophthalmologica. Volume II.** Edited by F. P. Fischer Utrecht, Netherlands; A. J. Schaeffer, Los Angeles, and Arnold Sorsby, London. Amsterdam, Netherlands: Dr. W. Junk, 1948.

This second edition of the "Documenta Ophthalmologica" is a welcome addition to literature on recent advances in ophthalmology. It is prefaced by a fitting tribute to the memory of Selig Hecht by George Wald.

Dynamics," Dr. V. Everett Kinsey, Boston; "A Critical Discussion of Experimental Exophthalmos," Dr. George F. Smelser, New York.

The attendance at the meeting was a tribute to the quality of the program, as well as to the efforts of the sectional secretary, Dr. A. E. Braley, and his organizational committee.

**Georgia Society of Ophthalmology and Otolaryngology.**—The annual meeting of the Georgia Society of Ophthalmology and Otolaryngology will be held at the General Oglethorpe Hotel in Savannah on March 4 to 5, 1949.

The distinguished lecturers and their tentative subjects are: "Management of Glaucoma," Dr. Paul A. Chandler, Boston; "Management of Cataract," Dr. Jack S. Guyton, Baltimore; "Allergy of the Upper Respiratory Tract," Dr. Oscar C. E. Hansen-Pruss, Durham, N. C.; "Management of Otologic Problems in Children and an Otologic Survey," Dr. Marvin F. Jones, New York; "External Diseases of the Eye and Dacryocystitis," Dr. Ralph O. Rychener, Memphis, Tenn.; "Problems in Laryngology," Dr. Fletcher D. Woodward, Charlottesville, Va.

**Association for Research in Ophthalmology.**—The annual meeting of the Association for Research in Ophthalmology will be held at the Warwick Hotel in Philadelphia, June 6 and 7, 1949.

Authors desiring to present papers at this meeting should submit the titles of their papers to James H. Allen, M.D., University Hospitals, Iowa City.

**Ophthalmological Society of Egypt.**—The annual meeting of the Ophthalmological Society of Egypt will take place at the Memorial Ophthalmic Laboratory, Giza, Egypt, on Friday and Saturday, March 4 and 5, 1949, at 9 a. m. Medical practitioners, oculists or others are cordially invited.

#### PERSONAL NEWS

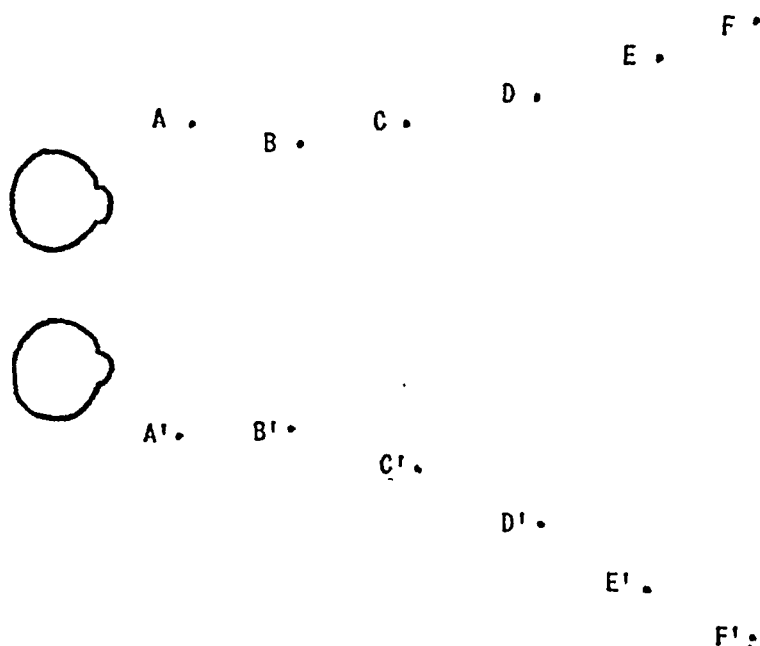
**Dr. J. C. McCulloch Awarded Reeve Prize.**—The University of Toronto Faculty of Medicine has announced that Dr. J. C. McCulloch has been awarded the Reeve Prize; this award is made for the best scientific research accomplished in any department in the faculty of medicine by one who has held an appointment on the staff for not more than five years.

Dr. McCulloch was awarded this prize for his investigations, in conjunction with Dr. R. J. P. McCulloch, entitled "A Hereditary and Clinical Study of Choroideremia"; this has added greatly to the knowledge of this previously obscure hereditary ocular condition. The disease was found in over 80 descendants of a family of 500 members who were studied.

Dr. J. C. McCulloch is ophthalmologist in chief at Toronto Western Hospital and was recently appointed associate in the department of ophthalmology, in the University of Toronto.

**Mathematical Analysis of Binocular Vision.** By Rudolf K. Luneburg. Price, \$2.50. Pp. 104. Published for the Dartmouth Eye Institute. Princeton, N. J.: Princeton University Press, 1947.

This work is, in the opinion of the reviewer, the most substantial advance in the mathematical theory of binocular vision which has been made in many years. Whether or not the concepts advanced will permit future improvement in the design of binocular microscopes, range find-



Set of pairs of vertical wires in Hillebrand's alley experiment.

ers, field glasses, slit lamps and other binocular instruments is, as Dr. Luneburg realizes, dependent on further experimental observations. These observations would be directed to the determination of what percentage of persons possess a visual space differing significantly from euclidean space.

It is the reviewer's thought that if the hypothesis is confirmed by further observation more immediate and feasible applications would be to orthoptic training, three dimensional motion pictures and television, particularly the last.

The basic thesis of the book is that visually perceived space is not Euclidean but is more readily described by the hyperbolic geometry of Lobachevski, although the applicability of Euclidean or Riemannian elliptic geometry in the instance of individual observers cannot be excluded.

In Euclidean space parallel lines are everywhere equidistant. Luneburg refers to Blumenfeld's repetition of Hillebrand's alley experiments as proof that visual space is not Euclidean. In alley experiments, the observer's head is fixed in a vertical position, and he is presented with two vertical wires,  $A$  and  $A'$ , one placed to the right and the other to the left of the midline between the two eyes, as shown in the figure.

Additional pairs of vertical wires movable in a horizontal plane are provided, and the observer adjusts them so that the "walls"  $B, C, D, A, E, F$  and  $B', C', D', A', E', F'$  appear either everywhere equidistant



The table of contents is as follows: "In Memoriam: Selig Hecht," G. Wald, New York; "Physiologic Optical Studies," A. von Tschermak-Seysenegg, Prague; "Physiologic Optics of the Visualization of Roentgenograms," W. Bronkhorst, Bilthoven, and J. ten Doesschate and F. P. Fischer, Utrecht; "Measurements of Fusion Frequency in the Clinic," R. Weekers and F. Roussel, Liège; "Mechanical Properties of the Tissues of the Eye," J. ten Doesschate and F. P. Fischer, Utrecht; "Apparatus and Method for Clinical Recording of the Electroretinogram," Gosta Karpe, Stockholm; "Early Diagnosis of Siderosis Retinae by Use of Electroretinography," Gösta Karpe, Stockholm; "Introduction to Experimental Trachomatology," L. Poleff, Rabat.

The general makeup of this volume is similar to that of volume I, but, in the opinion of the reviewer, the subject matter is not so well chosen. It is hoped that the next volume will contain reviews on branches of ophthalmology in which there has been considerable advance in the last few years, yielding information of practical value.

FRANCIS HEED ADLER.

**Optometry: Professional, Economical and Legal Aspects.** By H. W. Hofstetter. Price, \$6.50. Pp. 412, with 35 illustrations. St. Louis: C. V. Mosby Company, 1938.

"This book is intended as a reference and text for use in undergraduate courses in optometry to familiarize the student with various non-clinical aspects of the practice of optometry." The author states that he is "indebted to the American Optical Company for a grant which has enabled [him] to devote such time as was free from teaching duties toward completion of this edition." The book is of little use to medical men except to reveal the aims and methods of optometry. The author states the use of the title "doctor" by the optometrist rests on the feeling "that he earns the right to use it by inspiring confidence in the citizens of a community that he is qualified to do the things that an optometrist is expected to do. So long as the optometrist uses the title to keep himself classified as a member of the healing art in the same manner as a dentist uses his title, he has a reasonable claim to the use of the title."

The author endeavors to strengthen the optometrist's claim to special ability in refraction and defines the "ophthalmologist as a physician certified by the American Board of Ophthalmology. The oculist is a physician without special certification who limits his practice to care of the eyes. The Eye, Ear, Nose and Throat Specialist is a physician without special certification who limits his practice to care of the eyes, ears, nose and throat."

These excerpts will suggest that organized optometry has neither changed its methods nor elevated its sights to the standard of a profession which it claims to be. It is hoped that its leaders will reshape its practice to permit a confident discharge of obligations to its patrons and justify a participation in the various public health and general welfare activities.

RALPH I. LLOYD.

## PERSISTENCE AND HYPERPLASIA OF PRIMARY VITREOUS; RETROLENTAL FIBROPLASIA—TWO ENTITIES

ALGERNON B. REESE, M.D.

NEW YORK

CONSIDERABLE attention has been given to blindness of infants,<sup>1</sup> especially premature infants, due to a condition or conditions called by such various terms as retrolental fibroplasia, persistence and hyperplasia of the primary vitreous, remains of the tunica vasculosa lentis and congenital encephalo-ophthalmic dysplasia. All agree that there has been a large increase in the incidence of this type of blindness.

At the Institute of Ophthalmology, we have seen 202 cases and 128 of these have occurred in the past three years. At the Massachusetts Eye and Ear Infirmary<sup>2</sup> 165 blind preschool children are recorded as residing in Massachusetts, and in 108 of these the blindness is due to retrolental fibroplasia.

As the high incidence of the disease has occurred only in the past ten or more years, and as the disease prior to this period was extremely rare, ophthalmologists over the country have not all incorporated the diagnosis in their repertoire. It is difficult, therefore, to arrive at a true estimate of the incidence of the lesion, because all statistics must be based on reports on the eye from ophthalmologists. The United States Public Health Service<sup>3</sup> has no statistics on the subject. This is also

This work was supported by a donation from Mr. Charles B. Wrightsman.

From the Institute of Ophthalmology of the Presbyterian Hospital in the City of New York.

Read before the Section on Ophthalmology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 23, 1948.

1. (a) Terry, T. L.: Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens: I. Preliminary Report, *Am. J. Ophth.* **25**:203-204 (Feb.) 1942; (b) Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants: II. Report of Cases, *Arch. Ophth.* **29**:36-53 (Jan.) 1943; (c) Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Infants Born Prematurely: III. Studies in Development and Regression of Hyaloid Artery and Tunica Vasculosa Lentis, *Am. J. Ophth.* **25**:1409-1423 (Dec.) 1942; (d) Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants: IV. Etiologic Factors, *Arch. Ophth.* **29**:54-65 (Jan.) 1943. (e) Reese, A. B., and Payne, F.: Persistence and Hyperplasia of the Primary Vitreous, *Am. J. Ophth.* **29**:1-19 (Jan.) 1946. (f) Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, *Arch. Ophth.* **36**:387-444 (Oct.) 1946.

2. Personal communication to the author.

3. Personal communication to the author.

or everywhere parallel. The outcome of the experiment is that the walls are set neither equidistant nor parallel under either set of instructions to the observer but, rather, have the general shape shown in the figure. Furthermore, the instructions that the walls be made equidistant results (in general) in their placement outside the walls resulting from the instruction to make the walls parallel. As Luneburg says, this is "strong evidence" that visual space is hyperbolic, and not Euclidean.

Experiments at the Dartmouth Eye Institute with rooms, with variously curved walls and with variously curved windows, all of which, viewed binocularly, give the impression of the same rectangular room, can be adequately explained by the hypothesis that the "actual values" of elevation and horizontal deviation of the eyes "and especially the value of the convergence  $\gamma$  are insignificant for the visual sensation." As Luneburg correctly points out, "however, this theory leads us into difficulties when we try to understand the psychological fact of judging size independent of localization." An object first viewed at a distance of 1 meter and then at a distance of 10 meters appears to be of substantially the same size, although the area of its retinal image has varied by a factor of 100 to 1. This phenomenon, known as "size constancy," indicates that the human visual system can allow for, and hence must "perceive," distance. The existence of size constancy leads Luneburg to "the introduction of the convergence  $\gamma$  as a significant element of binocular vision." On first consideration, it may seem improbable that the "actual value" of convergence should be able to play a part in binocular vision, while the "actual value" of elevation or horizontal deviation of the eyes does not. It has been indicated (Irvine, S. R., and Ludvigh, E. J.: *Is Ocular Proprioceptive Sense Concerned in Vision?* ARCH. OPHTH. 15: 1037-1049 [June] 1936), however, that the ocular muscles lack proprioceptive sense and that human vision relies on "innervation sense." It is thus possible that the degree of convergence or the distance of an object may be "perceived," although the amount of contraction or relaxation of the internal and external rectus muscles is not.

Luneburg proceeds to the analytic derivation of the expressions for the walls of distorted rooms equivalent to rectangular rooms. He then asks which of the geometries of constant curvature, elliptic, Euclidean or hyperbolic, is best able to account for the phenomenon of size constancy. Luneburg finds that over the critical region of distances from 1 to 25 meters only the hyperbolic geometry can account for the relative constancy of the ratio between apparent and physical size. Luneburg then derives theoretic frontal plane horopters, assuming that hyperbolic geometry is the proper geometry for binocular visual sensations. These horopters resemble the Hering-Hillebrand deviations from the Vieth-Müller circles over the region  $\pm 25$  degrees from the midline between the eyes. However, at more eccentric positions the horopters deviate from the classic horopters. Further experimentation is, as Luneburg points out, necessary.

ELEK LUDVIGH.

more, there are indications that the incidence has increased not only in the past decade or more, but even more during the past few years.

From a study of our cases, in all of which examination was made with the child under general anesthesia, I believe that at least two different

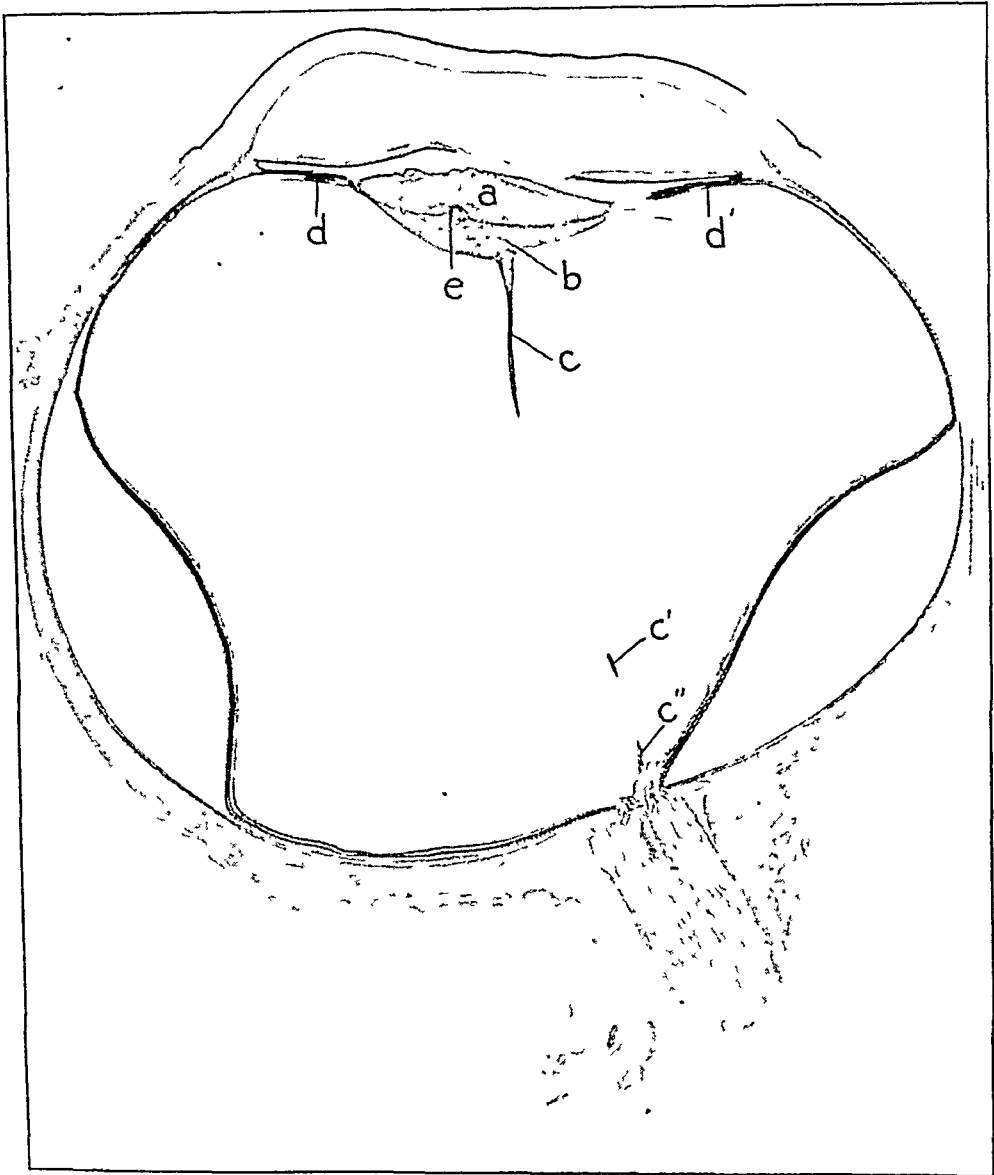


Fig. 1.—Section of an eye of a full term infant with persistence and hyperplasia of the primary vitreous. Back of the lens (*a*) can be seen the fibrous tissue (*b*), extending from which is seen the hyaloid artery (*c*). This artery is also seen at *c'* and at *c''* it is attached to the nasal side of the disk. The long ciliary processes are seen at *d* and *d'*. The posterior capsule of the lens shows a dehiscence at *e*. The retina contains all of its elements, and the detachment is an artefact.

conditions are now being confused. The one will be called "persistence and hyperplasia of the primary vitreous" and the other "retrolental fibroplasia."

true of many state and local organizations concerned with health statistics.

Figures on the incidence of the disease are available in five states. The reports from four of these states are as of April 1947.

The Division for the Blind, Department of Public Welfare, Chicago,<sup>4</sup> reported a total of 109 blind preschool children known in the state, and remarked, "A more adequate coverage of the state would, we feel, reveal considerably more cases." Of this total of 109 children, ophthalmologic reports were available for only 48. For 20 of these 48 children, retrolental fibroplasia was given as the cause of blindness.

The New Jersey State Commission for the Blind<sup>4</sup> reported 96 cases of blindness in preschool children, all of which were covered by ophthalmologic reports, and in 28 of that number retrolental fibroplasia was given as the cause of blindness. Since this report, the New Jersey State Commission has listed a total of 135 cases under their supervision. This rise, within the last nine months, may be real or apparent or both.

The New York State Commission for the Blind<sup>4</sup> reported 115 cases, of which 93 were covered by ophthalmologic reports; 20 of them were cases of retrolental fibroplasia.

The Wisconsin School for the Visually Handicapped<sup>4</sup> reported that 58 visually handicapped preschool children were known to the field service of the Department of Public Instruction, and added, "Information included on causes of blindness is not too reliable, as less than 40 per cent of the cases are based on direct medical reports." Eight of the 58 children had retrolental fibroplasia.

The Division of the Blind, Department of Education of the Commonwealth of Massachusetts<sup>5</sup> reported as of Jan. 1, 1948 that 148 cases of blindness in preschool children were recorded and that in 82 of these a diagnosis of retrolental fibroplasia had been made.

The figures quoted from the Institute of Ophthalmology and from the Massachusetts Eye and Ear Infirmary give too high an incidence of retrolental fibroplasia because both these institutions have manifested particular interest in the disease. The figures available from the four states give too low an incidence of retrolental fibroplasia because many ophthalmologists are not diagnosing this condition, which has only recently assumed importance, and the statistics depend on their certificates. Ophthalmologic reports covering a larger number of preschool children and better case-finding methods of the organizations interested in the blind would lead to the discovery of many more blind preschool children. I feel that a fair estimate is that one third of all cases of blindness in preschool children now are due to retrolental fibroplasia. Further-

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4. Lowenfeld, B.: *The Blind Preschool Child*, New York, American Foundation for the Blind, Inc., 1947, vol. 3, pp. 13-15.

5. Personal communication to the author.

macular region (fig. 2) show it to be well formed. In this fibrous tissue back of the lens most of the derivatives of mesodermal tissue can in some instances be identified. In addition to connective tissue, smooth muscle, cartilage, fat and blood vessels are sometimes present.

In some cases there is a dehiscence in the posterior capsule of the lens over the site of the fibrous tissue. This may cause a swelling of the lens and, therefore, an advancement of the iris-lens diaphragm so that these structures touch the posterior surface of the cornea (fig. 5), causing a dense corneal opacity, which begins in the central portion and extends to the periphery.

*Embryology.*—The primary vitreous, which is vascularized mesoderm, is shown in figure 3 *A* at the fourth month of fetal life. Figure

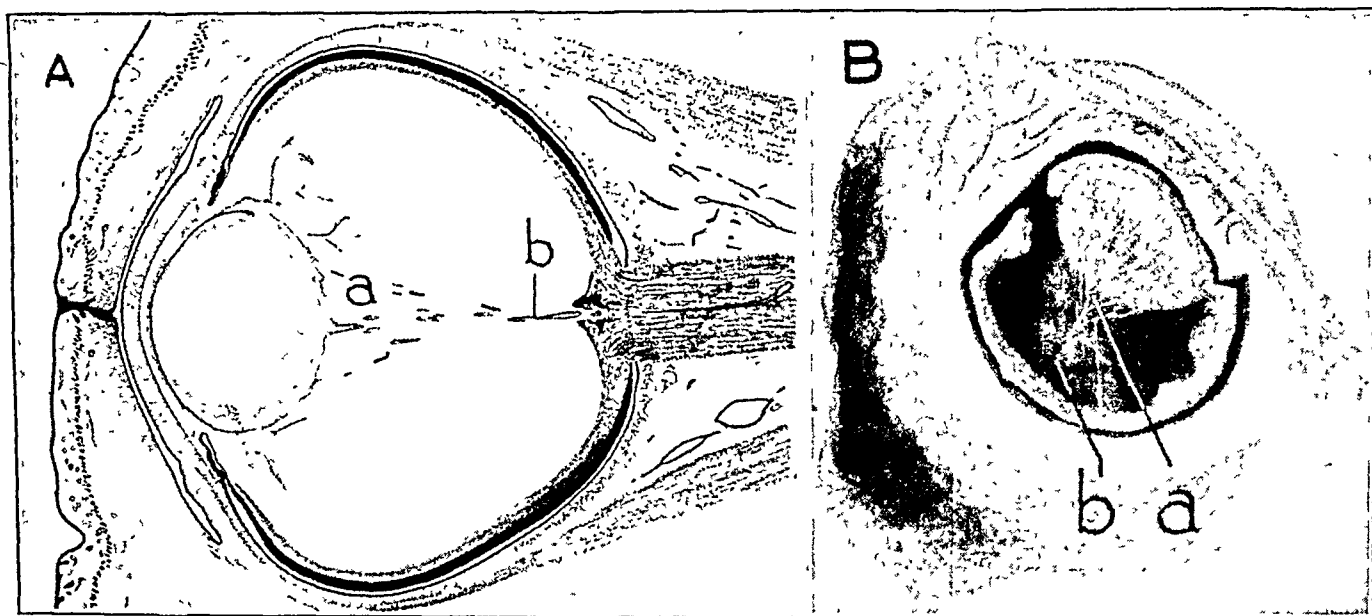


Fig. 3.—*A*, section of normal eye of a 4 month fetus showing the loose vascularized fibrous tissue (*a*) composing the primary vitreous. The hyaloid artery is seen at *b*.

This figure is taken from Bach, L., and Seefelder, R.: *Atlas zur Entwicklungsgeschichte des menschlichen Auges*, Leipzig, W. Engelmann, 1911-1912.

*B*, normal eye of 6 month fetus with a scleral window cut out in order that loose vascularized fibrous tissue (*a*) composing the primary vitreous may show. The hyaloid artery is seen at *b*. This specimen was loaned to me by Dr. Henry C. Haden.

3*B* shows the eye of a 6 month fetus with a scleral window cut out so that the primary vitreous is visible. The similarity can be noted between this specimen and that in figure 4, which is the eye of a 6 week old infant with a scleral window cut out so that the persistent hyperplastic primary vitreous can be seen.

*Clinical Features.*—Clinically, hyperplastic vitreous is seen as dense opaque tissue back of the lens (fig. 5). The tissue has a yellowish to pinkish hue and contains blood vessels, which usually radiate from the

## PERSISTENCE AND HYPERPLASIA OF PRIMARY VITREOUS

*Pathologic Characteristics.*—There is adequate pathologic material for study, as this condition is sometimes confused with retinoblastoma and the eye is therefore enucleated.

The histologic picture of this condition (figs 1 and 2) is characterized by the presence of dense fibrous tissue along the posterior surface of the lens, being thickest in the central portion and thinning toward the periphery. It is usually associated with persistence of the hyaloid

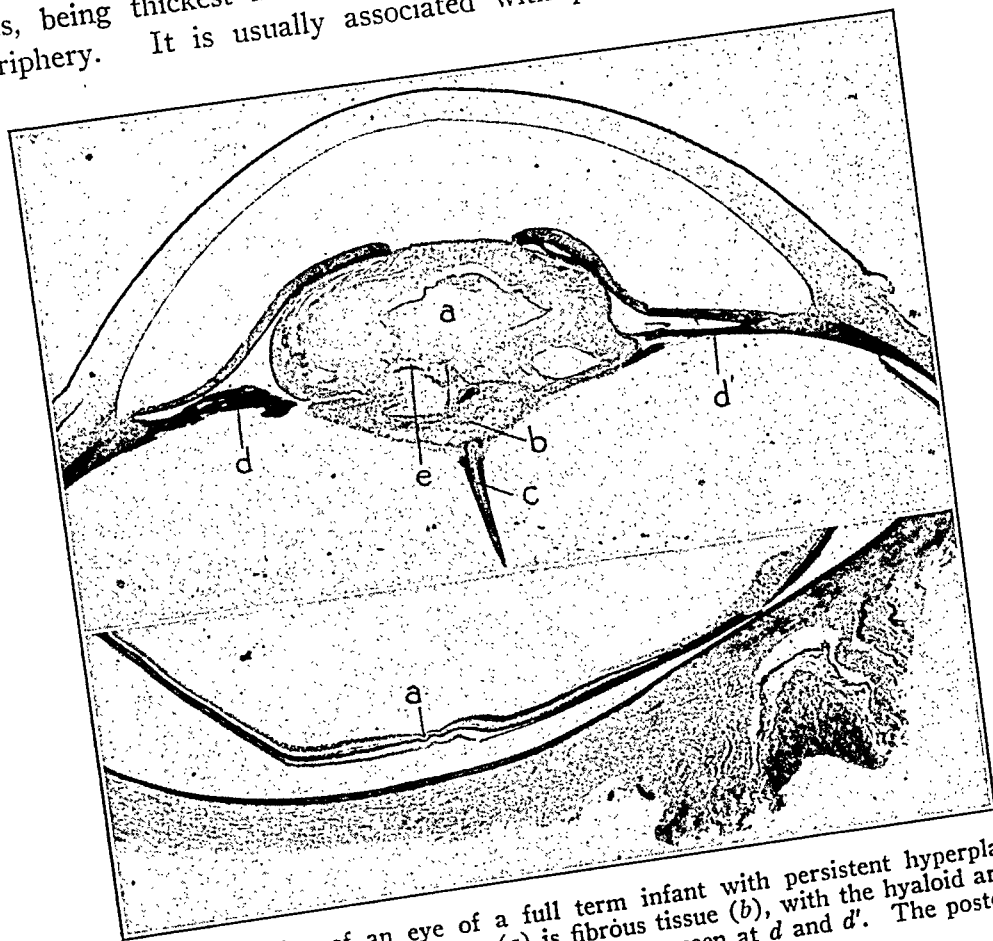


Fig. 2.—Section of an eye of a full term infant with persistent hyperplastic primary vitreous. A, back of lens (a) is fibrous tissue (b), with the hyaloid artery (c) attached to it. The long ciliary processes are seen at d and d'. The posterior capsule of the lens is open at e.

B, posterior sector of the same eye, of which A is the anterior sector. The retina shows normal structure, with a well formed fovea showing at a. The detachment of the retina is an artefact.

artery, which extends to the optic disk. Characteristically, also, the ciliary processes are elongated and extend into the periphery of the fibrous tissue. In some instances the periphery of the retina also extends as a fold far forward, even into the pars optica, and histologically it has however, is not detached in the pars optica, and histologically it has all its elements and appears capable of functioning. Sections through the

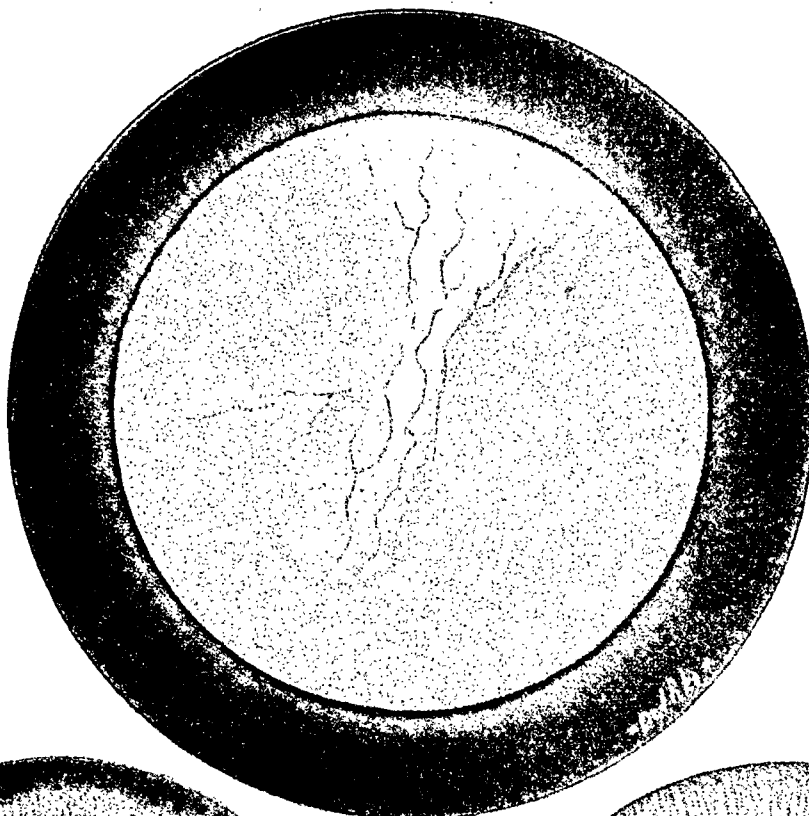


FIG. 12

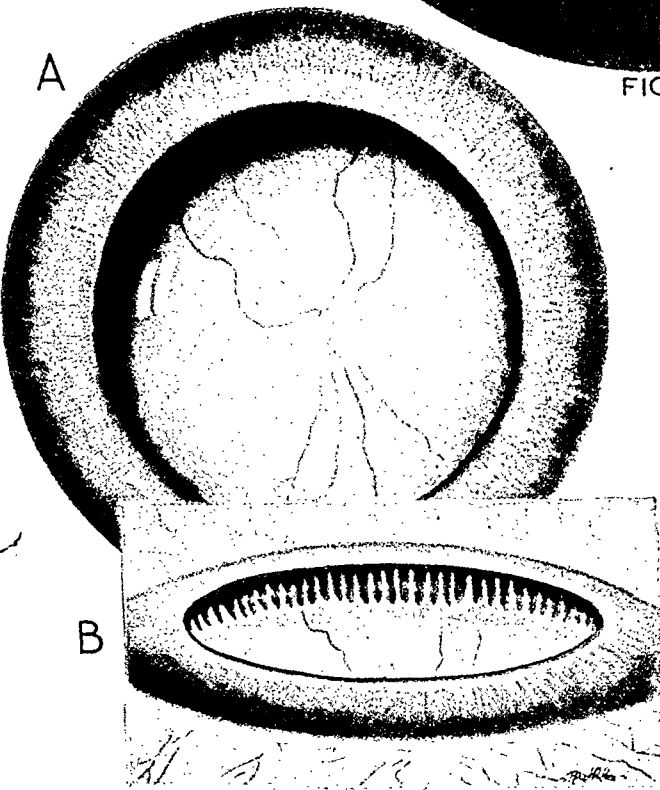


FIG. 5

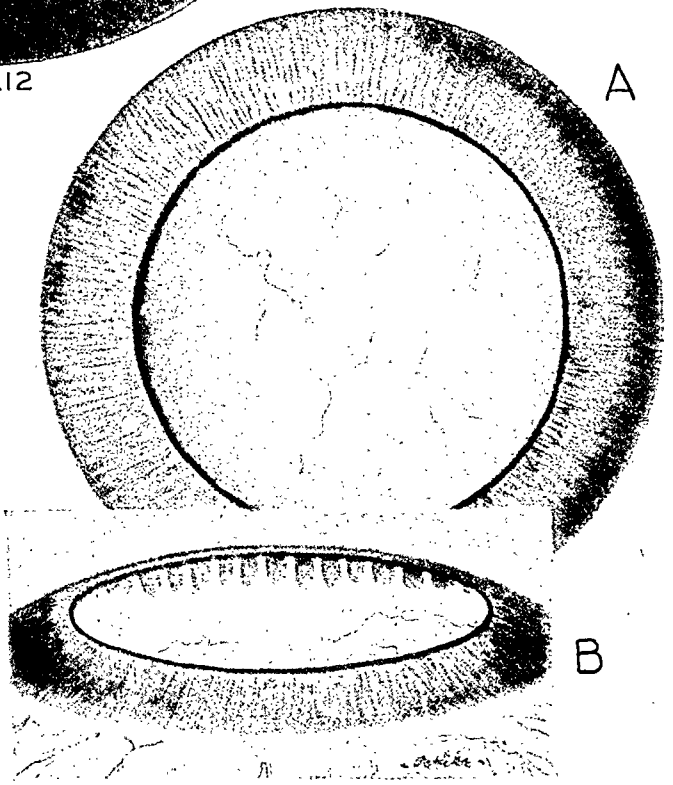


FIG. 11

Fig. 5.—Clinical appearance of persistent hyperplastic primary vitreous. *A*, anterior view; *B*, peripheral view, showing long ciliary processes.

Fig. 11.—Clinical appearance of retrolental fibroplasia in eye of infant born after six and one-half months' gestation. *A*, anterior view; *B*, peripheral view, showing the finger-like projections (dentate processes).

Fig. 12.—Clinical appearance of retrolental fibroplasia in the eye of an infant born after seven months' gestation. The fibrous tissue along with a retinal fold extends from the periphery above toward the equator of the lens, but for the most part it extends posteriorly through the vitreous to the disk, which is drawn inward, giving it a coloboma-like appearance.



center. The opacity decreases in density around the periphery, where as a result the fundus or the fundus reflex may be seen. The long ciliary processes are usually also visible. Hemorrhage may be seen in the fibrous tissue.

There are lesser degrees of this lesion (figs. 6 and 7), down to its least manifestation, which is the so-called Mittendorf dot.

The condition usually occurs in full term infants who develop normally, and it generally affects only one eye. The affected eye may

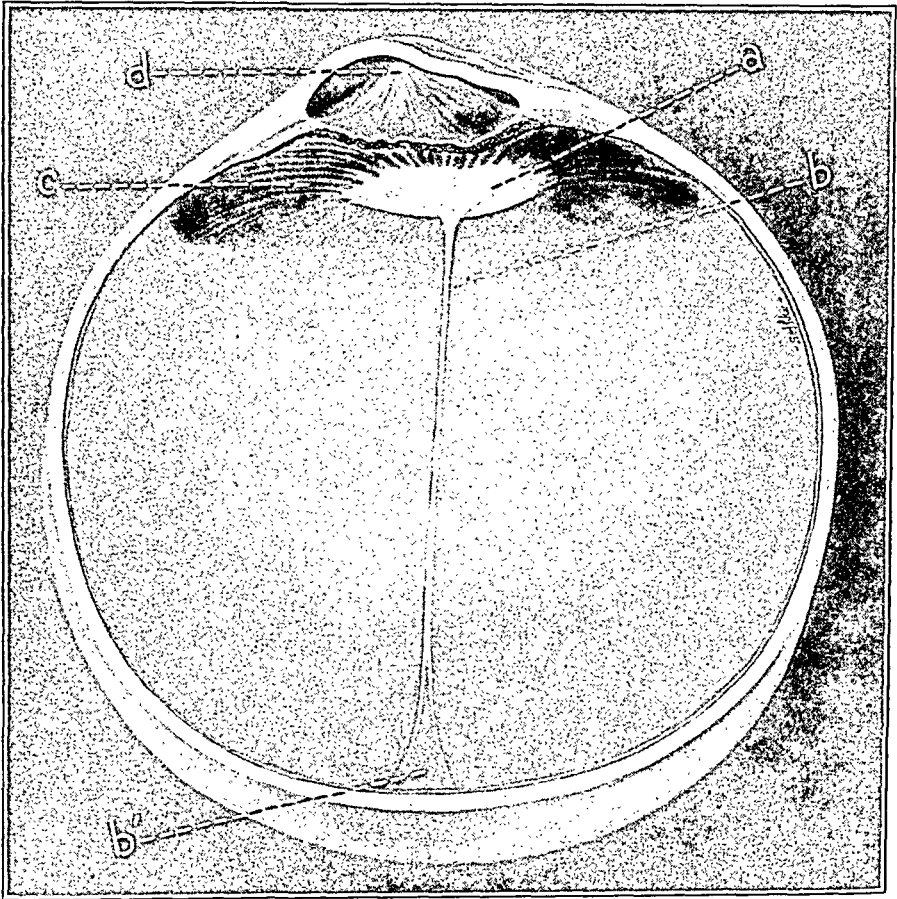


Fig. 4.—Eye of a full term infant with a scleral window cut out to show the persistent hyperplastic primary vitreous. The following features are noted: the fibrous tissue back of the lens, at *a*; the hyaloid artery, at *b* and *b'*, and the long ciliary processes, at *c*. At *d* the iris-lens diaphragm has advanced forward, touching the posterior surface of the cornea and thereby producing a corneal opacity. Sections of the eye showed that this forward extension was due to an opening in the posterior capsule of the lens, which caused a swelling of the lens.

be of the same size as the normal fellow eye, but often it is slightly smaller.

The presence of this lesion is usually detected immediately after birth, so that these patients are seen when they are only a few days to a few weeks old.

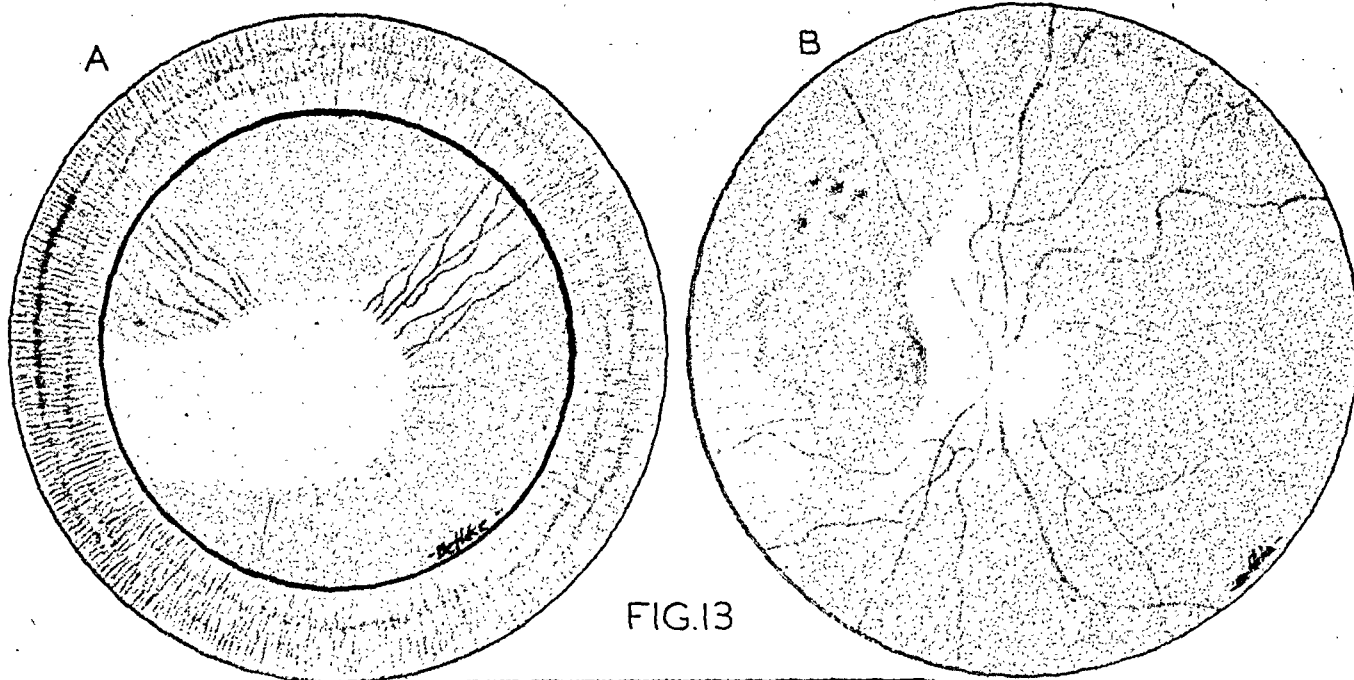


FIG.13

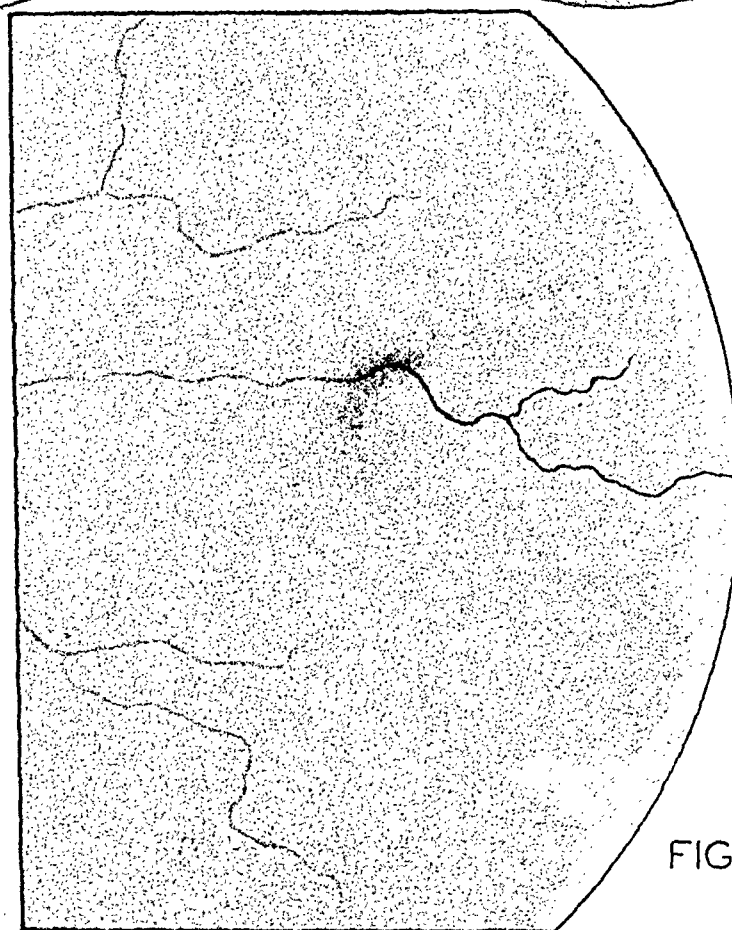


FIG.14

Fig. 13.—Clinical appearance of retrolental fibroplasia in the eye of an infant born after six months' gestation.

*A* shows tongue of fibrous tissue along with a retinal fold extending from the periphery toward the equator of the lens, but for the most part posteriorly in the vitreous toward the disk.

*B*, appearance of fundus of the fellow eye, showing the pale, milky appearance, the attenuated vessels, the pigmentary change and the fibrous tissue on the nasal side of the disk. No tissue was seen around the periphery of the lens.

Fig. 14.—Clinical appearance of retrolental fibroplasia in the eye of an infant born after seven months' gestation. Far in the periphery, around the base of the vitreous on the temporal side, can be seen the grayish white fibrous tissue. There is a small, flat detachment of the retina. A similar lesion was present in the fellow eye.



There can be no doubt that the lesion is congenital. The fibrous tissue back of the lens has the pyramidal shape of the primary vitreous and is observed at birth or shortly thereafter. As this tissue has no connection with the ciliary body it could not be situated where it is as the result of an acquired lesion. If it were an acquired lesion, there would of necessity be some connection between the tissue and the surrounding ciliary body or the peripheral portion of the retina. Furthermore, the fact that the hyaloid artery is almost constantly present points to the congenital nature of the lesion.

Moreover, the tissue back of the lens is thickest in the central portion and thinnest at the periphery; were it acquired from the surround-

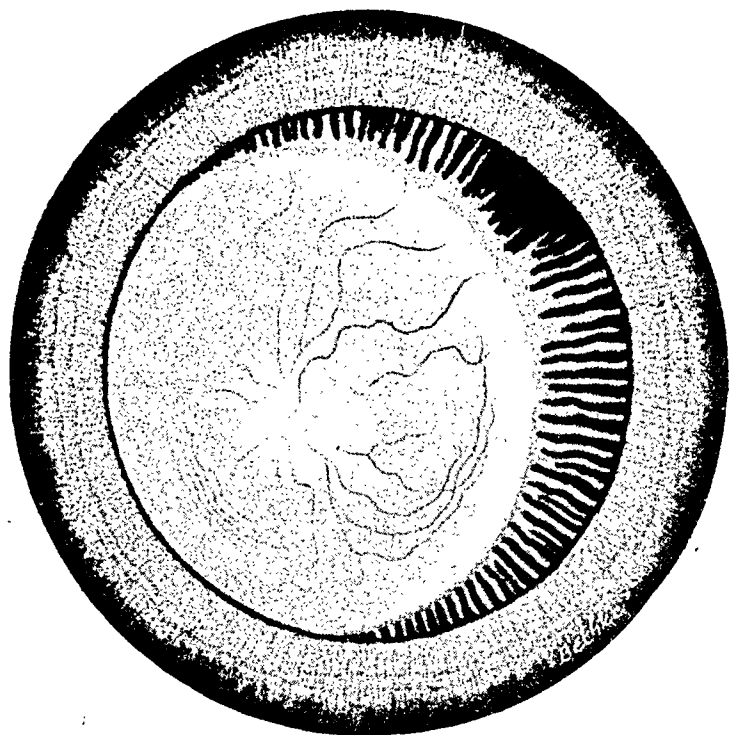


Fig. 6.—Clinical appearance of a persistent hyperplastic primary vitreous of a lesser degree than that shown in figure 5.

ing vascular structures of the ciliary body, choroid or retina, the peripheral portion would be the thicker. The fibrous tissue sometimes contains cartilage and all other mesodermal elements, and it is obvious that these are not present as a result of changes in acquired organized fibrous tissue.

Eyes with hyperplastic vitreous are sometimes enucleated with the clinical diagnosis of retinoblastoma, not only because of a similar clinical appearance but also because the lesion appears unilaterally at birth in full term infants. It is important to make the correct differential diagnosis and thus avoid unnecessary enucleation, for an eye with hyperplastic vitreous has the potentiality of vision. Even the fovea



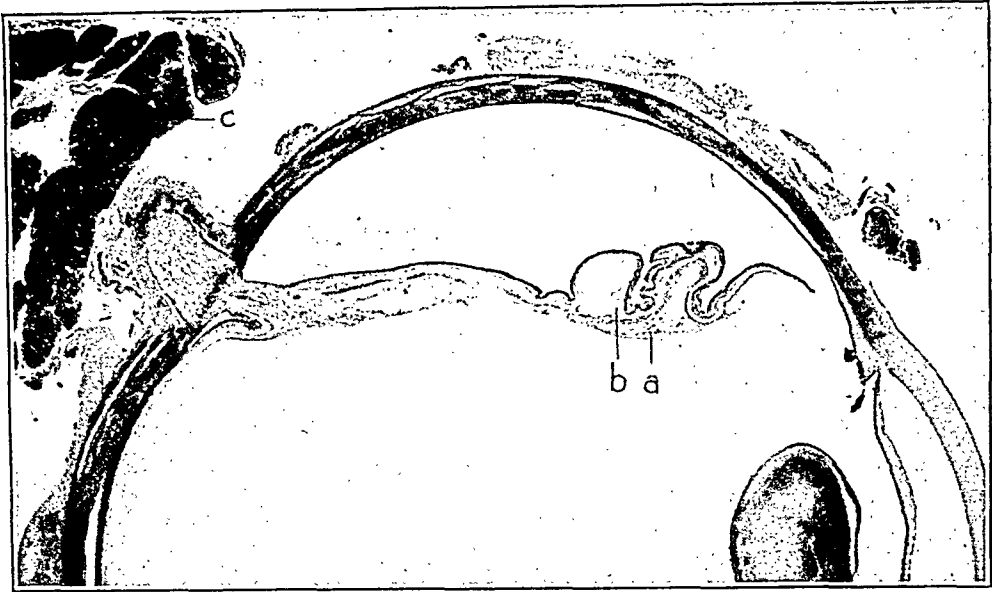


Fig. 8.—Section showing retrolental fibroplasia in an eye of an infant born after six months' gestation (see text for history). Along the surface of the retina, particularly near the ora serrata, is vascularized fibrous tissue (a), in which is some hemorrhage (b). The contraction of the organized fibrous tissue has caused a detachment of the retina and traction on the optic nerve head. Some strands of fibrous tissue extend from the hemangiomatous tissue to the posterior surface of the lens. A hemangioma which was responsible for exophthalmos during life is seen in the orbit at c. The fellow eye showed a similar lesion of hemangiomatous tissue along the surface of the retina, particularly in the periphery.

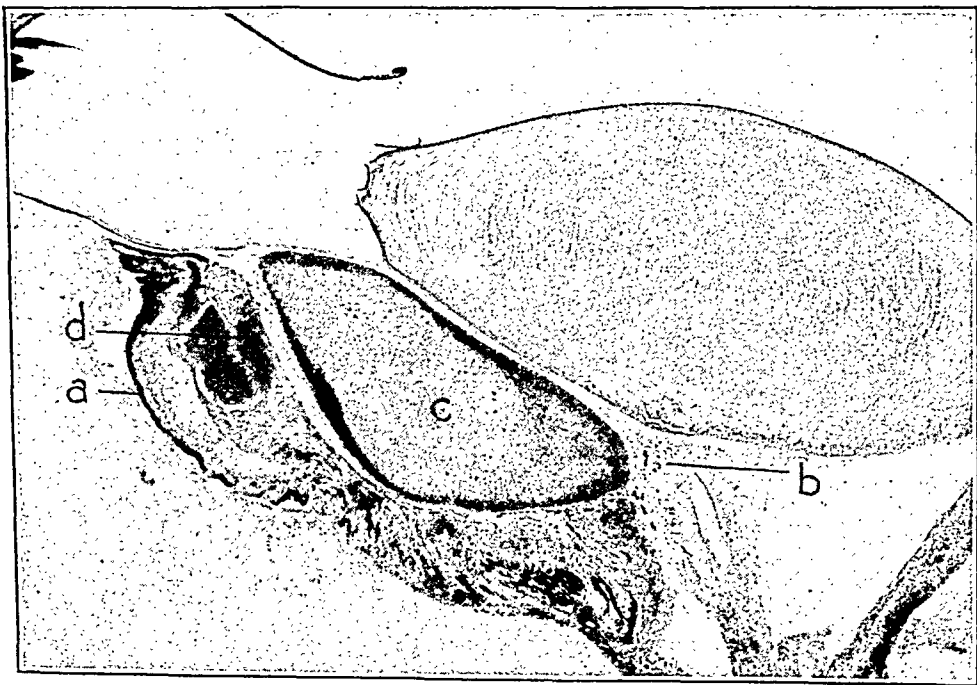


Fig. 9.—Section showing retrolental fibroplasia in an eye of an infant born after six and one-half months of gestation. Over the surface of the detached retina (a), near the ora serrata, is a great deal of vascularized fibrous tissue (b) with hemorrhage (c) and organization (d).

appears intact. Theoretically, one should be able to remove the opaque tissue back of the lens and obtain a functioning eye. The treatment will be discussed later.

#### RETROLENTAL FIBROPLASIA

*Pathologic Features.*—There is a scarcity of good pathologic material for study of this condition, as the clinical appearance does not

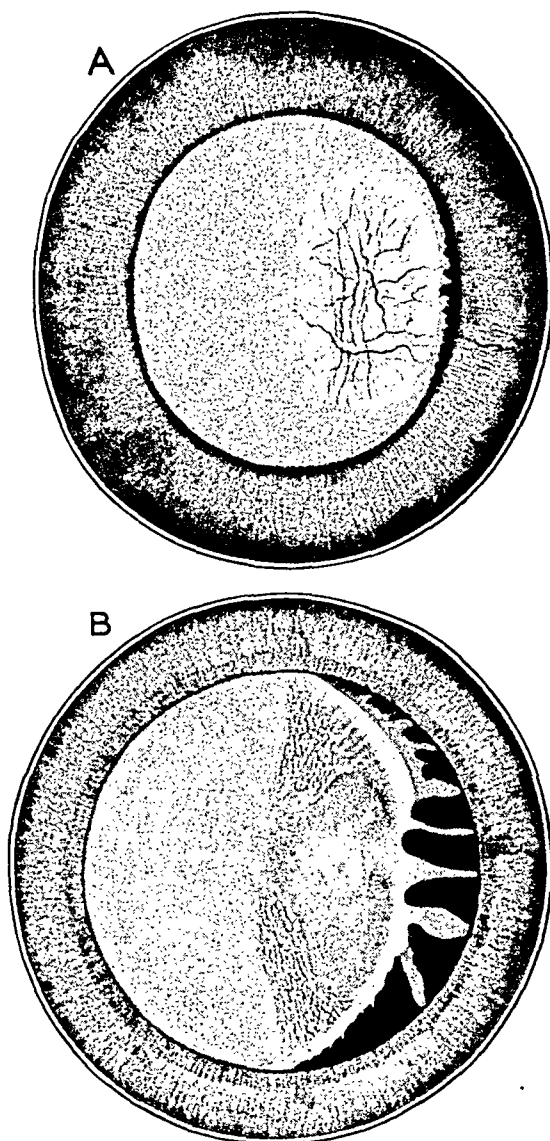


Fig. 7.—Clinical appearance of persistent hyperplastic primary vitreous of a lesser degree than that shown in figure 6.

*A*, appearance of lesion when patient was 9 days old; *B*, appearance of the same lesion when the patient was 7½ years old.

closely simulate retinoblastoma, and the other associated factors, such as prematurity and microphthalmos, help in making the correct diagnosis. The eye, therefore, is seldom enucleated unless there is an

The resultant contraction leads to detachment of the retina, which seems invariably to be present. The fibrous tissue extends over the posterior surface of the lens, but for the most part it courses posteriorly into the vitreous in the direction of the disk. In the more advanced stages, the retina is completely detached, and there are old and recent hemorrhages in all stages of organization. Particular attention is called to the case illustrated in figure 8. This case furnishes the earliest microscopic changes in retrolental fibroplasia and seems to give a good indication of the nature of the early changes in this disease.<sup>6</sup>

The history is as follows: Of twins born three months prematurely, one lived and no abnormalities were noted except for typical retrolental fibroplasia in both eyes. The other twin, who weighed 1 pound 10 ounces (737 Gm.) at birth, showed, when several weeks old, an exophthalmos of the right eye. Examination of the fundi was not done with the patient under general anesthesia. After many attacks of cyanosis with cessation of respiration, the infant died, and an autopsy was performed.

The autopsy observations were as follows: hemangiomas of the pharynx, right carotid body and right orbit, both retinas and the adjacent vitreous and the choroid plexus of the fourth ventricle; extramedullary blood formation in the spleen, liver, adrenal glands, kidneys and lymph nodes; splenomegaly; lobular pneumonia of the lower lobe of the right lung; accessory adrenal gland attached to the fallopian tube, and patent foramen ovale.

Microscopic examination of the eyes showed the following changes:

Right Eye (fig. 8): The retina was detached over one-half the globe, and over the retinal surface, particularly the portion detached, there were many blood vessels with a moderate amount of supporting tissue. There was some vitreous hemorrhage, which apparently came from the angiomatous tissue along the surface of the retina. The hemorrhage had become partially organized, and the contraction of this tissue had led to detachment of the retina. At no point could excessive blood channels be seen in the fiber layer of the retina. Behind the globe there was a large nonencapsulated hemangioma containing large blood-filled sinuses surrounded by hyperplastic endothelial cells.

Left Eye: The retina was in position, but along its entire surface were small blood vessels, occurring either as a thin layer or as localized clumps, with relatively little supporting tissue. In places these blood vessels over the retina lay along the surface of the internal limiting membrane, while elsewhere they appeared in the nerve fiber layer.

(This case was cited in a previous article [Reese and Payne <sup>1e</sup>]).

*Embryology.*—On the basis of the available pathologic material and the clinical characteristics, it is probable that the basic lesion in this condition is the persistence of some of the vascular primary vitreous in the region of the base of the vitreous. In the microscopic sections showing the earlier phases of the disease, this vascularized mesoderm can clearly be seen, and even resembles angiomatous tissue in some

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6. This eye was obtained for microscopic examination because the patient, who was one of twins, died at the age of 3 months. The twin of the patient lived and has typical retrolental fibroplasia in each eye.



advanced pathologic condition, with complete retinal detachment and secondary glaucoma. Then the true picture is masked. We have available for microscopic study 3 globes showing the lesion in a relatively early stage. In addition, I have studied all the material available at the Army Institute of Pathology, and Dr. Bertha Klien has permitted me to study her excellent material.

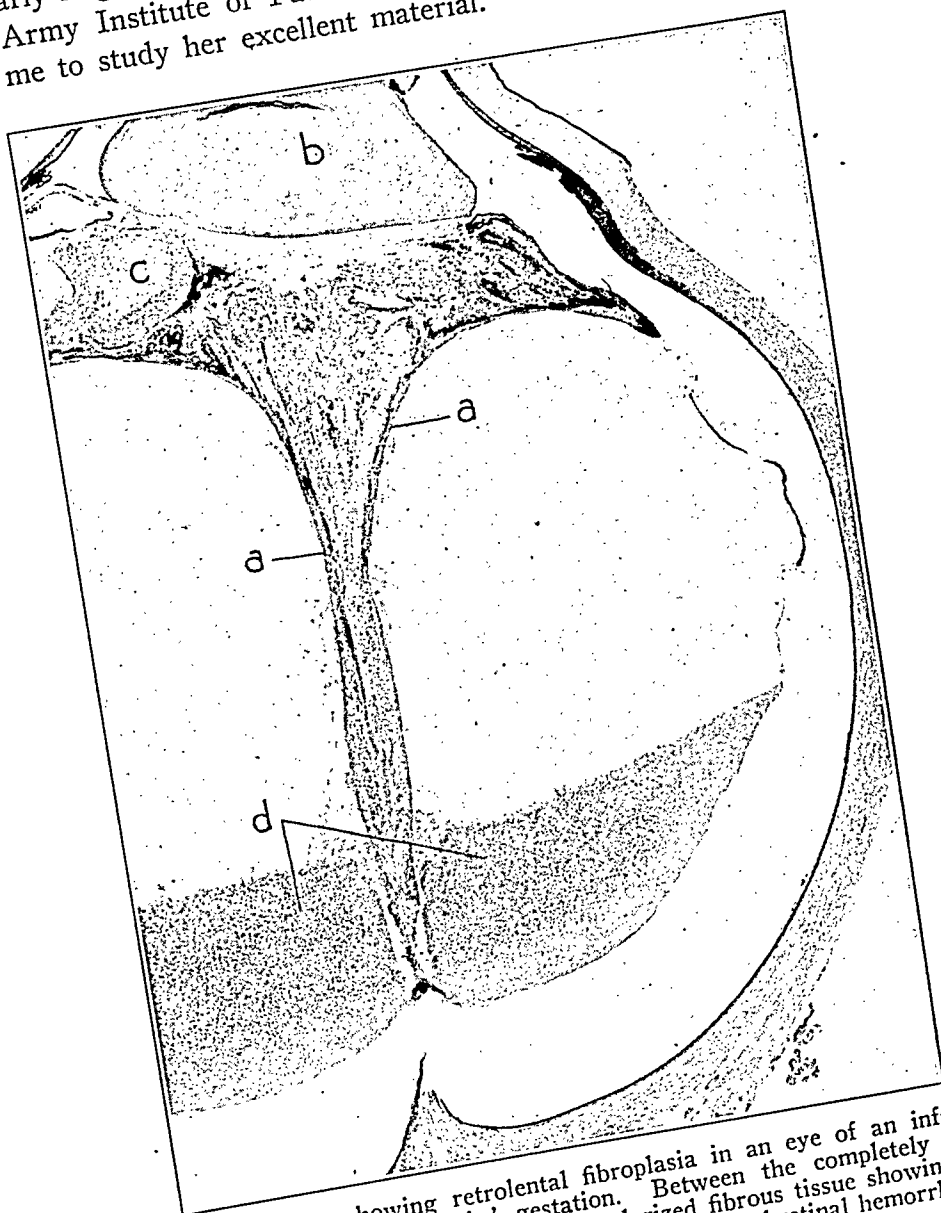


Fig. 10.—Section showing retrolental fibroplasia in an eye of an infant born after seven and one-half months' gestation. Between the completely detached retina (*a* and *a'*) and the lens (*b*) is a vascularized fibrous tissue showing hemorrhage and organization. A blood cyst is seen at *c* and subretinal hemorrhage at *d*.

The pathologic process (figs. 8, 9 and 10) is centered around the base of the vitreous. Here is found fibrous tissue rather rich in vascular channels. This tissue probably undergoes some hyperplasia, but its increase seems to stem mostly from hemorrhage and organization.

This manifestation of retrolental fibroplasia is certainly the same condition as that spoken of in the literature as congenital retinal fold, congenital falciform retinal fold or *ablatio falciformis congenita*. Guerry<sup>7</sup> stated that in cases of congenital retinal folds some authors have reported that the hyaloid artery, either the principal trunk or one of the *vasae hyaloideae propriae*, was attached to the fold or embedded firmly in its substance.

In the lesser manifestations of this lesion (fig. 14) it may be difficult to see the tissue around the base of the vitreous and the equator of the lens. In such cases it is absolutely necessary that one examine the patient while under general anesthesia, using a speculum to retract the lids and forceps to rotate the eye so that the most extreme portion of the periphery can be inspected. It is necessary sometimes to augment these measures by grasping the conjunctiva about 7 mm. from the limbus and pushing the sclera inward at the same time that the globe is rotated outward. In this manner a peripheral view can be obtained even as far as, or beyond, the *ora serrata*. The lesion is more frequently located temporally, and this is the area more accessible to indentation by the sclera.

A shallow anterior chamber is invariably present. This may become increasingly shallow, so that ultimately not only glaucoma ensues but the iris and lens are in apposition to the posterior corneal surface, particularly in the central area, and thus edema and an opacity of the cornea develop.

Glaucoma was present in about one third of the cases of retrolental fibroplasia. It is difficult, however, to establish definitely the presence of glaucoma, particularly if the tonometric reading is the sole criterion. I feel that the readings of the tonometer are not absolutely reliable in all cases, owing to the fact that the foot plate of tonometers is designed for corneas of adult size and the corneas of eyes with this condition show variations in size and curvature. The Souter tonometer should be the most reliable one to use. Digital palpation should also be reckoned in the final estimate. It is surprising, however, how well these eyes tolerate an increase in the intraocular pressure without showing ectasia of the globe. Some eyes seem to withstand an increase in intraocular pressure for an indeterminate time without developing buphthalmos. The cause of the glaucoma seems to be connected with the extremely shallow anterior chamber but malformation of the filtration angle is probably also a factor.

Eyes with fibroplasia are usually somewhat microphthalmic, but frequently they have a corneal diameter of 10 mm. or more and appear

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7. Guerry, DuP., III: Congenital Retinal Folds, *Am. J. Ophth.* **27**:1132-1135 (Oct.) 1944.

instances. This tissue does not seem to be in the retina but is definitely internal to the retina. It is from this vascular tissue that the hemorrhages and subsequent organization and contraction stem.

It must be assumed that an important embryologic feature of this condition is the adherence of this persistent vitreous to the adjacent inner layer of the optic cup. Over this layer the secondary vitreous fails to form, and therefore the retina is detached. The subsequent hemorrhage, organization and contraction lead to further retinal detachment.

*Clinical Features.*—All the clinical observations on which this paper is based were made on patients after the parents had suspected that something was wrong with the infants' eyes. They were made, therefore, on patients from 2 months of age on, and none from birth.

The lesion presents itself in various degrees of development, and this gives a wide range to its clinical manifestations. The condition usually manifests itself (fig. 11) as gray, opaque to translucent, tissue in the anterior portion of the vitreous and back of the lens. The lesion is somewhat vascularized and frequently shows hemorrhage or its sequelae, such as hemosiderosis, giving a greenish tint. The tissue is thickest and most opaque around the periphery in the region of the equator of the lens, especially on the temporal side and above.

Far in the periphery of the opaque tissue, serrations are frequently seen (fig. 11 *B*). These seem to be due in some instances to dentate processes of the opaque tissue, but in other instances the appearance is given by the ciliary processes, which are visible. In the first instance the serrations are the actual finger-like projections of the opaque tissue, whereas in the second instance serrations appear only as such between the valleys of the ciliary processes. It is my feeling that in cases of hyperplastic vitreous the actual ciliary processes are usually seen, whereas in the cases of fibroplasia it is the dentate processes that are usually seen.

The lesion may manifest itself primarily as a peninsula of opaque tissue in the periphery, especially temporally and above (figs. 12 and 13). This tissue radiates out over the posterior surface of the lens in part, but mostly it extends backward into the vitreous toward the optic disk. In the tissue there may be blood vessels, and in rare instances the number and character suggest an angiomatous element. Hemorrhage may be noted in the tissue. There is retinal detachment, the degree of which varies, but usually it manifests itself as a retinal fold confined chiefly to the quadrant in which the opaque tissue is seen. This retinal fold extends from the tissue toward the disk. Sometimes the opaque tissue obscures the underlying detachment. The disk is drawn out toward the detachment, giving it a colobomatous appearance with abnormally arranged blood vessels.

of hyperplasia. Ultimately, these factors lead to a completely detached retina, which is pulled by contracting fibrous tissue across the anterior portion of the vitreous. Clinically, therefore, the fibrous tissue is viewed just back of the lens and the detached retina lies back of this and sometimes can be seen through the interstices of the fibrous tissue. If the eye, with the patient under general anesthesia, is moved backward and forward with forceps, different levels of opacity in and back of the lens can often be appreciated by parallax. An opacity in the lens will move with the eye; opaque tissue just back of the lens will move against the eye; still another opaque tissue farther back of the lens will move more rapidly against the eye than the more anterior tissue.

I do not believe one can say that the matrix of this lesion is not present at birth without examining the patient while under general anesthesia, and with dilated pupils, using a speculum to retract the lids and forceps to rotate the eye so that the extreme periphery of the fundus may be inspected. Under the best of conditions there is still 4 mm. of fundus in the adult eye which is not accessible to view with the direct ophthalmoscope. In a newborn baby, even under the ideal conditions stated, I doubt whether it is possible to obtain a view beyond the equator of the globe, certainly not this far, without general anesthesia. Inductions of general anesthesia in a newborn premature infant is not feasible, but we hope to develop a method of heavy sedation which will permit an adequate examination. It seems to me that those who believe that the lesion is acquired must give sufficient proof that at least the matrix of the lesion is not present far in the periphery of the fundus, a condition which is indicated by all available pathologic material, as well as by the clinical manifestations.

There is still other evidence that retrolental fibroplasia is essentially a congenital lesion than that afforded by the pathologic material and the clinical behavior. The affected eyes are usually somewhat microphthalmic, and they frequently show a pupillary membrane arising from the collarette of the iris. Sometimes congenital anomalies are present elsewhere and there is an increased incidence of hemangioma of the skin, which is certainly a congenital lesion.

Sometimes the lesion regresses sufficiently to permit a view of the fundus in a case in which previously not even a fundus reflex had been visible. In the few instances in which this has occurred the retina was detached but did not show any angiomatous changes. The explanation for this regression is not clear. It may be predicated on absorption of the hemorrhagic element.

A feature of retrolental fibroplasia which should be mentioned is the high incidence of hemangioma of the skin in the affected patients. A hemangioma of some degree was noted in approximately 25 per

to be of about normal size for the age of the child. After glaucoma has persisted for some time, buphthalmos develops.

Atrophy of the iris, posterior synechias and the sequelae of exudate in the pupil and over the iris may be present. In some of the cases a pupillary membrane of a congenital nature, arising from the collarette of the iris, is present.

Fibroplasia usually affects both eyes and is of about the same degree and type in the two eyes. Occasionally the lesion is of a rather pronounced degree in one eye with the fellow eye showing a lesser degree, or even no opaque tissue, but an abnormal-appearing fundus (fig. 13). In all cases whenever the fundus is visible, it shows definite changes. These changes, which are of a pale, rather milky color, consist of slight, diffuse pepper pigmentation, which occasionally is marked and more or less localized; attenuated blood vessels, especially the arterioles, which are seen as mere threads; white sheathing of some vessels, especially the veins, and mild colobomatous changes of the disk, where the blood vessels show abnormal arrangement.

The lesion is characteristically seen in premature infants but may occur in full term infants. Thirteen of our cases were of full term infants. The incidence is higher in premature infants with the lower birth weights, especially 2,000 Gm. or less. Mental retardation and lack of normal physical development may occur. Nystagmus and microcephaly are sometimes present. The condition occurs in one or more of twins or triplets in from 10 to 15 per cent of cases.

There is no doubt that the lesion progresses after birth. Terry<sup>1a,b</sup> mentioned cases in which he observed the eyes shortly after birth, at which time he could not see anything abnormal in the media or the fundus, but later typical retrolental tissue appeared. This observation has been confirmed and amplified by Owens and Owens<sup>8</sup> and, later, by Unsworth.<sup>9</sup> I have seen numbers of cases in which the fibroplasia was so slight that the fundus could be well seen, only to have the view of the interior of the eye completely obscured later by the increase in extent and density of the retrolental tissue.

Retrolental fibroplasia is usually not noted until about the third to the fifth month after birth. I believe, however, that in all instances at least the matrix of the lesion is present at birth. This is seen around the equator of the lens and at the base of the vitreous. The basic congenital lesion is the remains of some angiomatous mesoderm from the primary vitreous, and from this tissue hemorrhage occurs, resulting in organization and retinal detachment, with perhaps an element

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8. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, *Tr. Am. Acad. Ophth.* (1947) **53**:18 (Sept.-Oct.) 1948.

9. Unsworth: Personal communication to the author.

and Australia, tell me that they do not encounter the condition except in a rare, sporadic case. Furthermore, in the fundi of the patients there are clinical manifestations over the areas accessible to examination which indicate that choroiditis of a mild nature has existed. This manifests itself as a diffuse, mild pigmentary disturbance. Some of the eyes having retrolental fibroplasia show evidence also of iridocyclitis. This manifests itself as posterior synechias, atrophy of the iris and the sequela of exudate around the pupillary margin of the iris. Moreover, in the mothers of these patients there is the high incidence of vaginal bleeding during pregnancy, and in some, the evidence of systemic infection of some kind during pregnancy. The latter may consist in a history of fever or of intercurrent infection, such as brucellosis, rubella or ulcerative colitis.

Instances of mild clinical, or even subclinical, infections of the mother affecting the offspring are known to exist. Toxoplasmosis is a subclinical infection of the mother which produces in the offspring chorioretinitis, as well as congenital anomalies. Roentgenograms of the skull in 12 of our cases of retrolental fibroplasia revealed in 1 case a punctate calcification in the brain identical with that seen in toxoplasmosis. Measles, and perhaps other virus diseases, in the mother can produce abnormalities in the offspring. The mother of 1 of our patients had rubella about the second month of pregnancy. There must still be other clinical and subclinical infections of the mother which act in similar fashion. It seems reasonable, therefore, to postulate that in retrolental fibroplasia a maternal infection of some nature is responsible for the variations in the incidence in different localities, for the vaginal bleeding, and thus the premature birth, and for the signs of inflammation such as chorioretinitis and iridocyclitis, in the eyes of the offspring. As pediatricians now save premature infants which would previously have been lost the sequela of this maternal infection in the infant now manifests itself as an increased incidence of a lesion which formerly appeared only sporadically. The increased incidence might also be attributed, in part at least, to an increase in the prevalence of some maternal infection.

Warkany and Schraffenberger<sup>12</sup> produced retrolental fibrous tissue and other congenital anomalies in the offspring of rats by feeding the mothers a diet lacking vitamin A.

The fact that premature infants have anemia, sometimes rather severe, for about the first three months may be significant.

Two features of the condition suggest that prematurity per se is important. These are the relatively high incidence of retrolental fibroplasia in twins and triplets and the not infrequent association of the

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12. Warkany, J., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Vitamin A Deficiency, *Arch. Ophth.* **35**:150-169 (Feb.) 1946.

cent of the cases. By the term "hemangioma" I mean not telangiectasis but an actual elevated, and sometimes pedunculated, tumor. The lesions may be extensive and multiple. They may be located in or under the skin anywhere over the body. They are present at birth, and they may enlarge and then regress. This process of involution is interesting and manifests itself as a steady shrinkage in the size of the lesion with wrinkling of the overlying skin. It is due apparently to a spontaneous sclerosis, which is seen first in the central portion of the lesion.

In the Hemangioma Clinic of Memorial Hospital for the Treatment of Cancer and Allied Diseases,<sup>10</sup> 56 mothers of infants and young children having cutaneous hemangiomas were interviewed. An attempt was made to establish any relation of the vascular abnormality in these infants to prematurity, to evidence of maternal infection during pregnancy or to retrolental fibroplasia. No such connection could be determined. Hess, Mohr and Bartelme<sup>11</sup> found hemangiomas of the skin in 8 of 250 prematurely born children, or in 3.2 per cent. They found hemangiomas of the skin in 2 of 156 full term siblings, or in 1.3 per cent. This difference in the incidence of hemangioma in premature and in full term infants does not seem significant, but the incidence of hemangiomas of the skin in premature infants with retrolental fibroplasia is definitely higher than in premature infants in general.

Another feature of interest, and probably of significance, is the fact that the mothers of these children gave a history of vaginal bleeding during pregnancy in approximately 30 to 35 per cent of the cases. In some instances the bleeding warranted hospitalization. Sometimes it was frequent throughout pregnancy, and sometimes it preceded the precipitous birth.

*Etiologic Factors.*—One can only speculate on possible causative factors. I think the lesion is essentially congenital, and therefore I look to the mother as the medium. Those who believe the lesion to be acquired naturally view the postnatal period of the infant with suspicion.

There is some evidence indicating that the disease may result from a maternal infection of some nature. In support of this it can be said that the incidence of the disease seems to vary in different localities. The incidence of retrolental fibroplasia during the last eight years has been found to average 18 per cent of all premature births in one Boston hospital,<sup>2</sup> while in some other localities the incidence seems lower. My colleagues in other countries, including France, Austria

10. Unpublished data.

11. Hess, J. H.; Mohr, G. J., and Bartelme, P. F.: *The Physical and Mental Growth of Prematurely Born Children*, Chicago, University of Chicago Press, 1934.

described in the past <sup>14</sup> as metastatic retinitis, intrauterine endophthalmitis and iridocylitis, congenital falciform retinal fold, opaque membrane behind the lens (Collins and Mayou, 1925), shrunken fibrous tissue cataract (Collins and Mayou, 1925), congenital connective tissue formation in the vitreous chamber (Collins and Mayou, 1925) and fibrous tissue cataract (Mann, 1937).

Both hyperplasia of the vitreous and fibroplasia have in common the persistence of the primary vitreous as the basic congenital lesion. An important difference, however, exists between the two. In the case of persistence and hyperplasia of the vitreous the primary vitreous remains *in toto* and the secondary vitreous forms, so that the primary vitreous occupies its normal position in a funnel-shaped fashion back of the lens. In other words, there has been merely a persistence of the primary vitreous with hyperplasia. In the case of retrolental fibroplasia only a portion of the primary vitreous remains in the region of its base. The important feature seems to be that this persistent primary vitreous is adherent to a portion of the inner layer of the optic cup. As the secondary vitreous forms, it tends to compress and isolate the primary vitreous. This occurs everywhere but in the region where the adhesions have taken place, and here the retina becomes detached. In addition, there may be hemorrhage from the persistent vascular primary vitreous, leading to organization, contraction and further retinal detachment.

Ida Mann <sup>15</sup> in discussing the nature of so-called congenital falciform retinal folds, postulated such an adhesion between the primary vitreous and the inner layer of the optic cup and stated that it must occur at about the 13 mm. stage, which would be about the fifth to the sixth week of embryonic life.

It is conceivable that such an adhesion could be produced by an intrauterine inflammation of the embryonic eye, and in this regard it is known that just at this embryonic period maternal infection can give rise to changes in the eyes of the offspring.

#### TREATMENT

Eyes with hyperplastic vitreous certainly have the potentiality of vision. The retina in these eyes is *in situ* and seems to contain all of its cellular elements; the fovea is well formed. Could the pupil be

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14. Collins, E. T., and Mayou, M. S.: Opaque Membrane Behind the Lens, in *Pathology and Bacteriology of the Eye*, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1925, p. 45; Shrunken Fibrous Tissue Cataract, *ibid.*, p. 47; Posterior Lenticonus, *ibid.*, p. 47; Congenital Connective Tissue Formation in the Vitreous, *ibid.*, p. 64. Mann, I. C.: Fibrous Tissue Cataract, in *Developmental Abnormalities of the Eye*, London, Cambridge University Press, 1937, p. 351.

15. Mann, I.: Congenital Retinal Fold, *Brit. J. Ophth.* **19**:641-658 (Dec.) 1935.



condition with toxemia of pregnancy. Both these factors predispose to premature birth.

#### COMMENT

As hyperplasia of the vitreous and retrolental fibroplasia are similar clinically, and as the clinical differential diagnosis of the two is seldom confirmed by microscopic examination, it is impossible to state the correct incidence. In our series I estimate that approximately over 90 per cent of the cases were of fibroplasia. I doubt whether the incidence of hyperplasia of the vitreous has changed over the course of years, but I am sure there has been a tremendous increase in the incidence of retrolental fibroplasia in the past decade or more. This may be due entirely or in part to the fact that pediatricians are saving premature infants who formerly would have been lost. Another factor may be an increased incidence of severe maternal infection, which is also responsible for the precipitous birth.

I believe that both these conditions have been confused in the past, that neither is a new manifestation and that both have always appeared sporadically and have been reported in the literature under various names. Hyperplasia of the vitreous<sup>13</sup> has been given various names, such as persistent thickened hyaloid artery with secondary changes (Nettleship, 1873), persistence and thickening of the posterior fibrovascular sheath of the lens (Collins, 1892; Pollock, 1923), atypical development of the anterior part of the vitreous with or without a persistent hyaloid artery (Collins, 1892), congenital membrane behind the lens (Parsons, 1902), persistence of remains of the tunica vasculosa lentis (Brückner, 1907), persistent posterior fibrovascular sheath of the lens (Lane, 1919), persistence of the embryonic fibrovascular sheath of the crystalline lens (Lent and Lyon, 1922), remains of the tunica vasculosa lentis (Gifford and Latta, 1923; Lloyd, 1931) and pseudophakia fibrosa of Czermak (Fuchs, 1923). I think that fibroplasia has been

13. Nettleship, E.: Vascular Cord Traversing Vitreous and Coexisting with Great Plastic Inflammation of Hyaloid, *Roy. London Ophth. Hosp. Rep.* 7:632-637, 1873. Collins, E. T.: Pseudo-Glioma, *Ophth. Hosp. Rep.*, London 13:361-394, 1890-1892. Pollock, W. B. I.: Case of Pseudoglioma Due to Persistence and Thickening of the Posterior Fibrovascular Sheath of the Lens, *Tr. Ophth. Soc. U. Kingdom* 43:263-272, 1923. Parsons, J. H.: Microscopical Section of Pseudoglioma Due to Congenital Membrane Behind the Lens, *ibid.* 22:253-254, 1902. Brückner, A.: Ueber Persistenz von Resten der Tunica vasculosa lentis, *Arch. f. Augenh.* 56:5-149, 1907. Lane, F.: Persistent Posterior Fibrovascular Sheath of the Lens, *Arch. Ophth.* 48:572-580 (Nov.) 1919. Lent, E. J., and Lyon, M. B.: Persistence of Embryonic Fibrovascular Sheath of the Crystalline Lens, *Am. J. Ophth.* 5:706-711 (Sept.) 1922. Gifford, S. R., and Latta, J. S.: Pseudoglioma and Remains of the Tunica Vasculosa Lentis, *ibid.* 6:565-571 (July 23) 1923. Fuchs, E.: Pseudophakia Fibrosa of Czermak, in *Text-Book of Ophthalmology*, ed. 7, Philadelphia, J. B. Lippincott Company, 1923, p. 650.

freed of the opaque tissue, there seems to be no reason that the eye would not have vision. In the cases of fibroplasia at least some degree of detachment of the retina is usually present. It is not certain, however, that the retina is always detached and, if detached in only one quadrant, whether or not it remains stationary or progresses. A patient, now 8 years old, with retrolental fibroplasia had the right eye enucleated because it was painful because of secondary glaucoma. The microscopic examination showed retrolental fibroplasia. In the left eye he has retrolental fibroplasia of the type shown in figure 12 and figure 13 *A*. There is a detachment of the retina in the quadrant of the eye occupied by the retrolental tissue. The retina elsewhere is still in situ, after eight years. Except for special schooling, the patient leads a normal life. This 1 case, therefore, indicates that a partial retinal detachment of this nature may remain stationary. In many of the cases it is impossible to say whether or not a detachment of the retina is present and, if so, to what degree. It is probable that in some cases of fibroplasia it is possible to salvage some degree of vision, but certainly in the majority of instances the vision is irretrievably lost because of complete retinal detachment.

In an effort to clear the pupillary area of the opaque tissue in certain indicated cases, I have done in the way of experimental surgery the operation shown in figure 15. This operation has been carried out only on selected eyes, i. e., eyes of about normal size for the age of the patient, eyes in which there is no visible evidence of retinal detachment, eyes in which there are no iris or corneal changes and in which no glaucoma is present.

The operation has been performed on 11 eyes, and in 3 cases there has been objective improvement in that the pupil has been sufficiently cleared to permit a view of the details of the fundus (fig. 16). An opinion, however, regarding the visual results must be reserved because of the age of the patients, the wishful thinking of the parents and the small number of eyes operated on. It can be said, however, that the operation is well tolerated and that no eye has been made worse. Further experience will be necessary in order properly to evaluate the procedure.

In cases of fibroplasia the retrolental tissue may be almost entirely on the temporal side with a much thinner portion nasally. In 1 case the thick tissue on the temporal side could be grasped with forceps and teased away; and, although it could not be drawn out through the scleral opening, it was dislocated nasally sufficiently to free the pupillary area over the nasal portion.

In the way of a surgical procedure, I first attempted repeated needlings, with the idea of getting rid of the lens substance and finally doing a de Wecker discission through the remaining retrolental tissue.

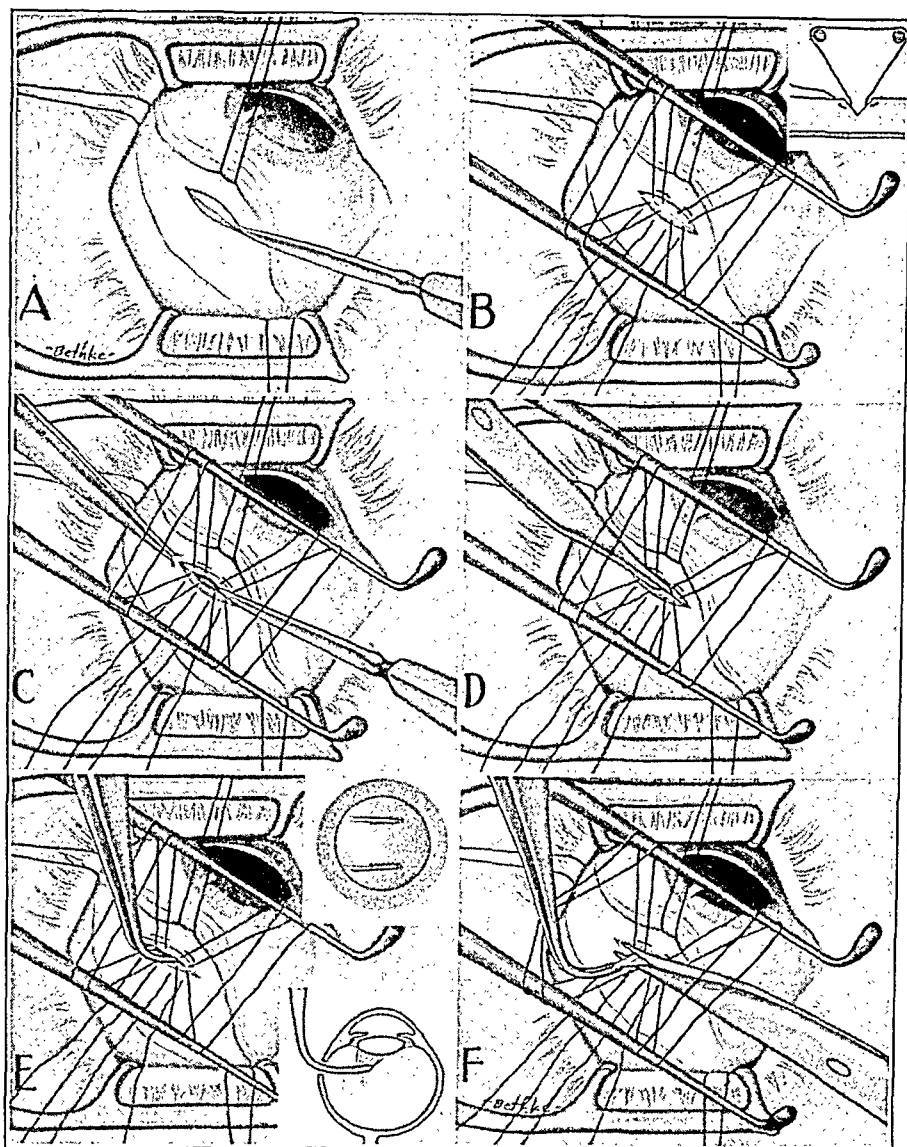


Fig. 15.—Excision of tissue back of the lens.

(A) An incision in the conjunctiva over the upper outer quadrant with silk traction sutures under the superior and lateral rectus muscles, as well as through the superficial lamellae of the sclera between 1 and 2 o'clock, 2 mm. from the limbus. An incision 4 mm. long is being made with the scalpel in the sclera for about one third of its thickness concentric with, and 4 mm. from, the limbus. An external canthotomy is usually necessary for adequate exposure. The incision in the sclera should be over the pars planum of the ciliary body and therefore anterior to the ora serrata.

(B) Two double-armed, 00000 plain surgical gut sutures are placed through the lips of the incomplete scleral incision. Two strabismus hooks serve not only for retraction of, but also for traction on, the sutures, so that at the site of the incision there is actual negative pressure. The insert shows the depth in the sclera to which the incision is made and the manner of placing the sutures.

(C) With negative pressure at the site of the wound, the incision is carried through the sclera at one site.

(D) With Stevens' scissors, the incision is enlarged 4 to 6 mm.

(E) With Terson's forceps, the wound is entered and the blades of the forceps are directed just posterior to the lens. By looking through the pupil, the blades can be seen magnified (see insert) and the tissue grasped under direct view.

(F) An attempt is made to tease the tissue loose and deliver it into the wound for excision. If the tissue is too fixed to deliver, one may free it nasally and pull it temporally sufficiently to free the nasal portion of the pupillary area without excising any of the tissue.

Sometimes the glaucoma advances sufficiently to create a painful, and obviously useless, eye, which is frequently buphthalmic; then, of course, enucleation is necessary.

We have tried roentgen therapy in 3 cases, employing the same technic as that which is used for retinoblastoma. The technic for retinoblastoma is designed for the maximum effect in the posterior half of the globe. The roentgen ray treatments have not helped in any way, but we feel that we have not given this treatment sufficient trial, and it is our plan to try in at least a few cases a modified technic designed to have the maximum effect in the region back of the lens.

Our hope seems brighter along the lines of prevention, and perhaps through roentgen therapy in the very early stages, before irrevocable damage has been done by progression of the lesion. It is possible that in affected infants the lesion could be detected in its very early stages by adequate examination. If the matrix of the lesion is noted, it may respond satisfactorily to roentgen therapy, as angiomatous tissue, particularly in infants, is known to be radiosensitive.

Dr. Frederick Blodi and Miss Lilly Kneiske gave help in this study.

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#### ABSTRACT OF DISCUSSION

DR. BRITAIN F. PAYNE, New York: The author has made a differentiation between "retrolental fibroplasia," a name given to post-lenticular fibrosis in infants under 3 pounds (1,360 Gm.) by the late Dr. T. L. Terry, of Boston, and "persistence and hyperplasia of the primary vitreous," a term devised by Dr. A. B. Reese and Dr. Frank Payne, of New York, for a similar condition. Although in the earlier stages of the disease the diagnostic points seem clear and definite, as the condition progresses the signs begin to merge, and it is most difficult to determine which condition exists. Sections of the affected eye may give a final clue, but an enucleation is not performed until secondary changes, such as glaucoma and retinal detachment, have occurred. Obviously, the microscopic picture is distorted by these secondary changes, and a true diagnosis is difficult. Little suggestion has been made as to the cause and prevention of these retrolental "changes" in this presentation. The actual mechanics involved in the formation of retrolental fibrosis are somewhat vague and have not as yet been described conclusively. It is possible that "primary vitreous," as generally accepted by most authorities, is actually "secondary vitreous" and forms after the indentation of the ocular cleft and the ingrowth of the hyaloid artery. The primary vitreous would be purely ectodermal and would consist of fibrils extending from the thickening lens placode to the beginning formation of the optic cup up to the 10 mm. stage. The tertiary vitreous would be entirely ectodermal, originating from the ciliary epithelium anterior to the ora serrata. If this reasoning is correct, it is possible that we are discussing persistence and hyperplasia of the secondary vitreous. Just

I carried out this procedure on 5 eyes in 5 patients. In the first place, the lens in these eyes did not act like a lens in a normal eye. After an extensive needling procedure, very little happened to the lens. It remained more or less transparent, did not swell and usually only a faint linear scar could be seen in the capsule. In short, this procedure was not at all satisfactory, and it was obvious that nothing could be accomplished by it.

The next procedure I tried was a vertical, through and through discission with a very sharp knife. The section went through the entire lens and the tissue back of it. I did this on 2 eyes in 2 patients. The complete through and through vertical discission was accomplished

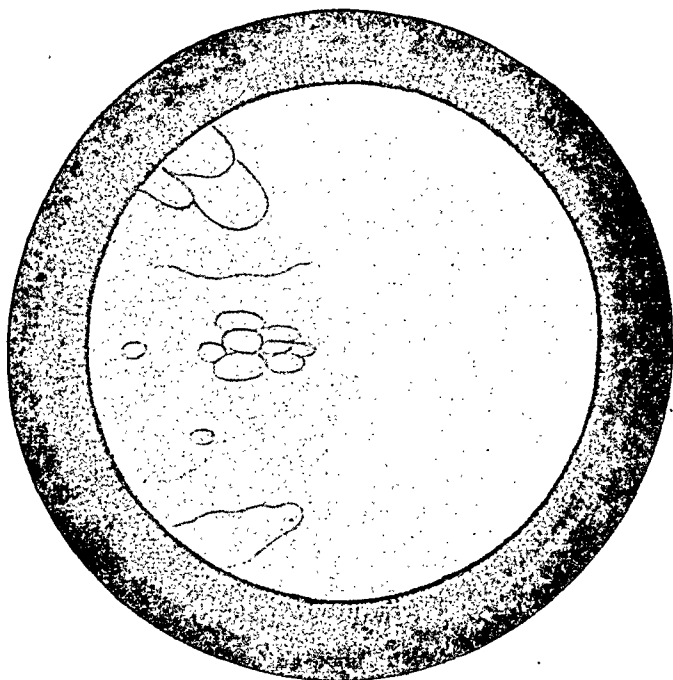


Fig. 16.—Appearance after excision of a sufficient amount of the temporal portion of the tissue to permit a view of the fundus in which no detachment of the retina was seen. There are vacuoles in the posterior cortex of the lens.

without any undue tug or difficulty. The results, however, were complete failures.

Glaucoma is a complication of both hyperplastic vitreous and fibroplasia and the possibility of its occurrence, therefore, is an issue that must be faced. As previously stated, it is not always easy to establish definitely the presence of glaucoma in these eyes because the tonometric readings are probably not always accurate. When glaucoma has been definitely established in eyes in which there may be some potential vision, I have usually tried to combat the glaucoma. Certainly, miotics are of no avail. The operation that I have found most satisfactory is the iridencleisis with sclerectomy.

DR. HAROLD FALLS, Ann Arbor, Mich.: I should like to take this opportunity to present to the audience preliminary work undertaken to establish the causation of the syndrome under discussion.

My colleagues and I have taken careful pedigrees of all children presenting retrolental fibroplasia whom we have seen. To date we have not discovered any evidence of a hereditary factor. No consanguinity has been found in the fifteen consecutive families studied. In conjunction with the taking of pedigrees, careful serologic studies of the families were made. We were primarily interested in the serologic observations because we desired to establish the correct relationship of the child to the family being studied. Secondly, we also desired to determine whether the Rh factor or serologic incompatibility played any significant etiologic role. Our excellent and meticulous serologist reported that no serologic incompatibilities had been encountered in a series of 15 children.

Since learning of the work of Drs. Owens and Owens on retrolental fibroplasia, we have had the opportunity of studying 1 child carefully from birth. This was a boy of Mexican ancestry, who was estimated to have been born after six and one-half months' gestation and to have weighed  $2\frac{1}{2}$  pounds (1,134 Gm.) at birth. The fundusoscopic examination, performed three and a half days after birth, revealed what I first thought could only be angiomatosis retinae. The superior and inferior temporal vessels (artery and vein) were huge and tortuous. Moreover, much anomalous branching of these vessels was seen in and about the extreme temporal periphery of the retina. The latter branching occurred in and on a grayish opaque membranous background. When observed over the passing months (nine), the apparently normal retina about and between the temporal vessels became gradually elevated, and slowly tension striae evolved. The vessels slowly diminished in size as they became incorporated in this new gray fibroplastic tissue. Moreover, after observable hemorrhage, the peripheral retina presented fibroplasia, which extended forward and centrally to approach and reach the temporal posterior surface of the lens bilaterally. At no time was there evidence of persistent hyaloid vasculature.

DR. WILLIAM C. OWENS, Baltimore: Three years ago, my co-workers and I decided that if we hoped to observe the clinical course of retrolental fibroplasia, we must observe premature infants from birth. During the past three years, we have been following up, in the Johns Hopkins Hospital, all the premature infants weighing less than 2,000 Gm. at birth. During this time we have observed the development of retrolental fibroplasia in many cases. In none was the disease present at birth. In all cases, the early course of the disease was characterized by dilatation of the retinal vessels with the formation of extensive edematous detachments of the retina. We were able to follow the complete regression of the tunica vasculosa lentis and the hyaloid artery. These structures had completely atrophied before the characteristic changes in the retinal vessels began. We have never seen retrolental fibroplasia develop from, or in, a persistent hyaloid artery or primary vitreous. The final picture has varied considerably, depending on the severity of the disease. We have observed during

why the fibrotic changes occur as the embryo develops and become exaggerated after birth is not known. Among the causes given are avitaminosis and intercurrent infections in the mother, but it is also thought that defective germ plasm plays an important role.

The problem of retrolental fibrosis has at least three aspects: 1. Prevention by selection of parents without ocular defects of this type. Let "fate" settle the problem of existence of these defective persons. Obstetricians and pediatricians should not be so zealous in preserving defective persons, of which this world has a sufficient quantity already. 2. Medical and surgical treatment. Therapy has not been successful, but there is hope that more progress will be made as time goes on. 3. The adjustment of the defective child and its family to the unpleasant situation of blindness and dementia. This may be the most important phase.

It is a great privilege to have been asked to discuss this excellent paper on a disease of the eye so little understood and about which so little can be done. The essayist has given us new insight.

DR. BERTHA A. KLIEN, Chicago: To me the most important statement in Dr. Reese's paper, and one which deserves more emphasis, concerns the frequent association of retrolental fibroplasia with multiple hemangiomas distributed over the body and the presence of angioblastic tissue behind the lens. Angioblastic overgrowth of the primary vitreous in response to some stimulus as yet unknown could occur at any time during gestation after the primary vitreous has started to form. Depending on this time element, the retina is involved in various ways, and different pictures of retrolental fibroplasia may be produced.

On the basis of the histologic material at my disposal, I believe that the matrix of the lesion is present at birth. Occurring early in embryonic life, hemangiomas like these may prevent, partially or completely, formation of the secondary vitreous. Angiomas forming later in remnants of the primary vitreous need not impede normal development of the eye, but may remain latent until some time after birth, when hemorrhages and the sequence of pathologic events, which Dr. Reese described so well, produce the final picture of retrolental fibroplasia.

A recent clinical observation may be of interest. The left eye of a 6½ month old infant, born two and a half months prematurely and weighing 2½ pounds (1,134 Gm.) at birth, was examined. When the infant was 3½ months old, a red area was noted in the left pupil. Six weeks ago, when I saw this patient in consultation with Dr. Kenneth Roper, there was behind the posterior pole of the lens a sharply defined, red area which had a knobby surface and was connected with a large blood vessel; this appeared to be a hemangioma rather than a hemorrhage. If further studies on retrolental fibroplasia should prove beyond doubt the primary role of hemangioma in its pathogenesis, regardless of the cause, as is strongly suggested by the observations of Dr. Reese, then Dr. Reese's modified roentgen therapy might be employed in a preventive manner to the eyes of extremely premature infants of mothers who have a history of systemic disturbances during pregnancy.

## HISTOPATHOLOGIC ASPECTS OF RETROLENTAL FIBROPLASIA

BERTHA A. KLIEN, M.D.

CHICAGO

MUCH has been accomplished by various authors (Reese,<sup>1</sup> Krause,<sup>2</sup> Ingalls,<sup>3</sup> Owens<sup>4</sup>) in clarifying the confusion of multiple terms and descriptions of apparently related conditions since Terry<sup>5</sup> first drew attention to a disturbance connected with prematurity to which he applied the not very appropriate, but in ophthalmologic circles now almost generally accepted, term of retrolental fibroplasia.

The pathogenesis of retrolental fibroplasia and of the conditions apt to be confused with it is of two principal, and essentially unrelated, varieties.

The first type, apparently not connected with maternal-fetal infection or premature birth, is characterized by arrest of embryonic growth, with or without aberrant growth of the involved tissues. There is commonly a familial or hereditary background, and more often than not the condition is unilateral. These genetically predetermined mal-developments may have their inception at any period of gestation and range from complete failure of primary retinal coaptation in more or less microphthalmic eyes to mere persistence of the hyaloid artery.

Retrolental fibroplasia is represented by the second group of cases. The bilateral occurrence, the extremely premature birth and the frequency of uterine bleeding during gestation cited by various authors suggest immediately a more direct and severer disturbance in the maternal-fetal relationship. This type of lesion is often not discernible at birth but becomes evident two to five months later.

On the basis of the histologic material at my disposal, I agree with Reese<sup>1</sup> that the matrix of the lesion is present at birth. The

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From the Department of Ophthalmology, Northwestern University Medical School.

1. Reese, A. B.: Persistence and Hyperplasia of Primary Vitreous (Tunica Vasculosa Lentis or Retrolental Fibroplasia), *Am. J. Ophth.* **29**:1, 1946.

2. Krause, A. C.: Congenital Encephalo-Ophthalmic Dysplasia, *Arch. Ophth.* **36**:387 (Oct.) 1946.

3. Ingalls, T. H.: Congenital Encephalo-Ophthalmic Dysplasia, *Pediatrics* **1**:315, 1948.

4. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia, Baltimore, Wilmer Residents Association, 1948.

5. Terry, T. L.: Fibroplastic Overgrowth of Persistent Tunica Vasculosa Lentis in Premature Infants, *Am. J. Ophth.* **25**:203, 1942.



their development the various examples of the disease shown by Dr. Reese and the discussers. During the inactive, late, stage of the disease, it is usual for the vessels in the membrane to decrease in size. We have also seen several cases in which the disease regressed spontaneously.

DR. ALGERNON REESE, New York: Dr. Payne stated that no mention has been made of the etiologic factors. Needless to say, the cause of retrolental fibroplasia is not known, but in the paper I included various possible causative factors, such as maternal infection, lack of vitamin A and anemia. Dr. Klien has shown us some excellent sections illustrating the pathologic changes. Her specimens seem to bear out the contention that the basic lesion in retrolental fibroplasia is persistence of the vascularized primary vitreous in the region of its base. I am grateful to Dr. Owens and Dr. Falls for their comments.

**Left Eye:** Through the dilated pupil a gray mass was visualized in the region of the nasal portion of the ora serrata. Above and below this mass and in the temporal part of the retina were large whitish areas. The optic disk was not visible, and there were only a few visible retinal vessels. These were seen best with a  $-14.00$  D. lens.

**General Physical Condition:** The general condition was normal except for a small umbilical hernia.

**Course.**—The diagnosis of bilateral retinoblastoma was made, and the right eye was removed. Radiation therapy of the left eye was carried out for the following five months. At the end of this period the left eye was removed also.

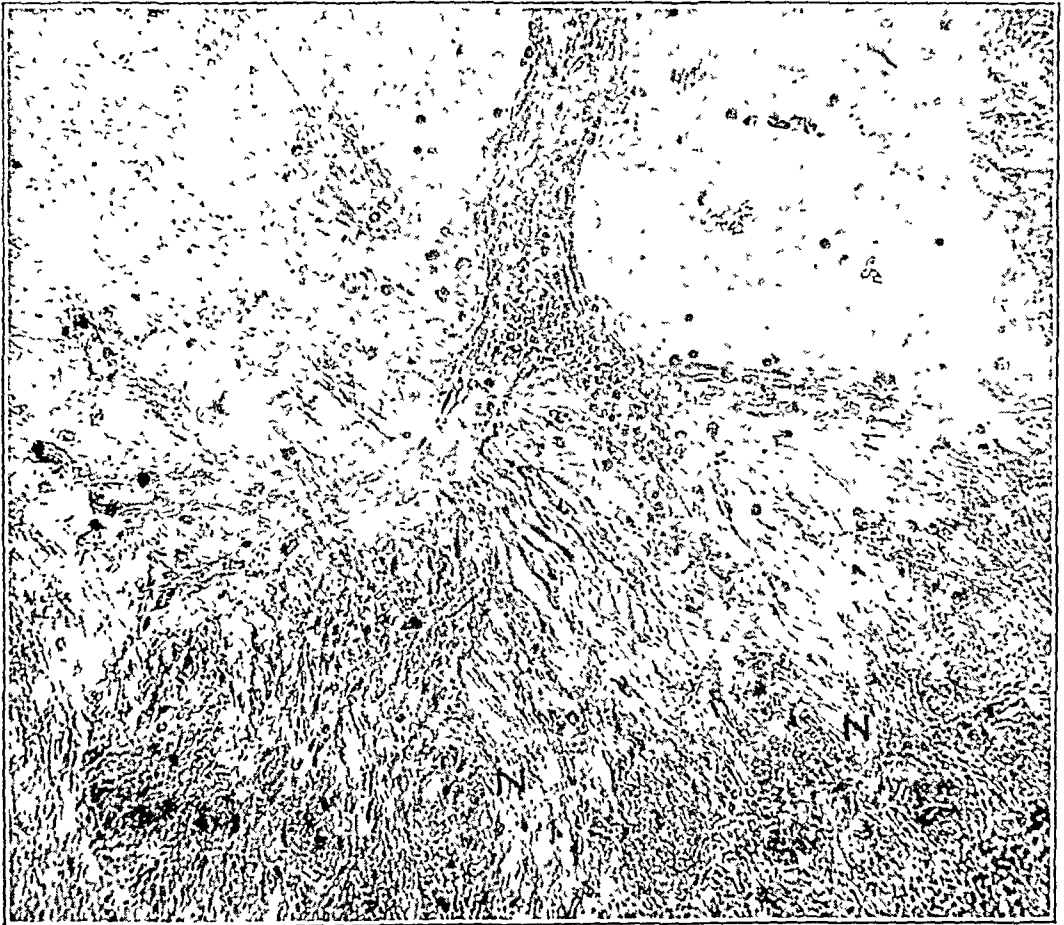


Fig. 2 (case 1).—Right eye: magnification of area *A* from figure 1, showing blood vessel in remnants of primary vitreous sending finger-like extensions into retina. *N* indicates nodules of proliferated endothelial cells.

**Histologic Study.**—Right Eye: The bulb measured 17 mm. in the sagittal, 18 mm. in the frontal and 19 mm. in the vertical diameter. The horizontal diameter of the cornea was 10 mm. The anterior chamber was shallow; the structures of the angle of the chamber were well developed, but a fan-shaped, delicate mesodermal tissue lay between the trabeculum and the anterior chamber. The iris was very cellular, with an undeveloped pattern of the anterior surface. The lens measured 4 by 5.5 mm.; the zonular fibers were well developed. The retina contained rosettes and pseudorosettes and was folded into a funnel-like mass, lying in the axial direction (fig. 1). Between the retina and the equatorial region of the

most important statement concerning the pathogenesis of retrolental fibroplasia, and one which deserves more emphasis, has been made in one of Reese's<sup>6</sup> recent papers. It concerns the frequent association of retrolental fibroplasia with multiple angiomas distributed over the body and the presence of angioblastic tissue behind the equatorial region of the lens, demonstrated histologically.

#### HISTOPATHOLOGIC REPORT

The histopathologic changes in 3 eyes with retrolental fibroplasia are discussed.  
 CASE 1.—R. E., a premature infant, was first seen at the age of 3½ months.

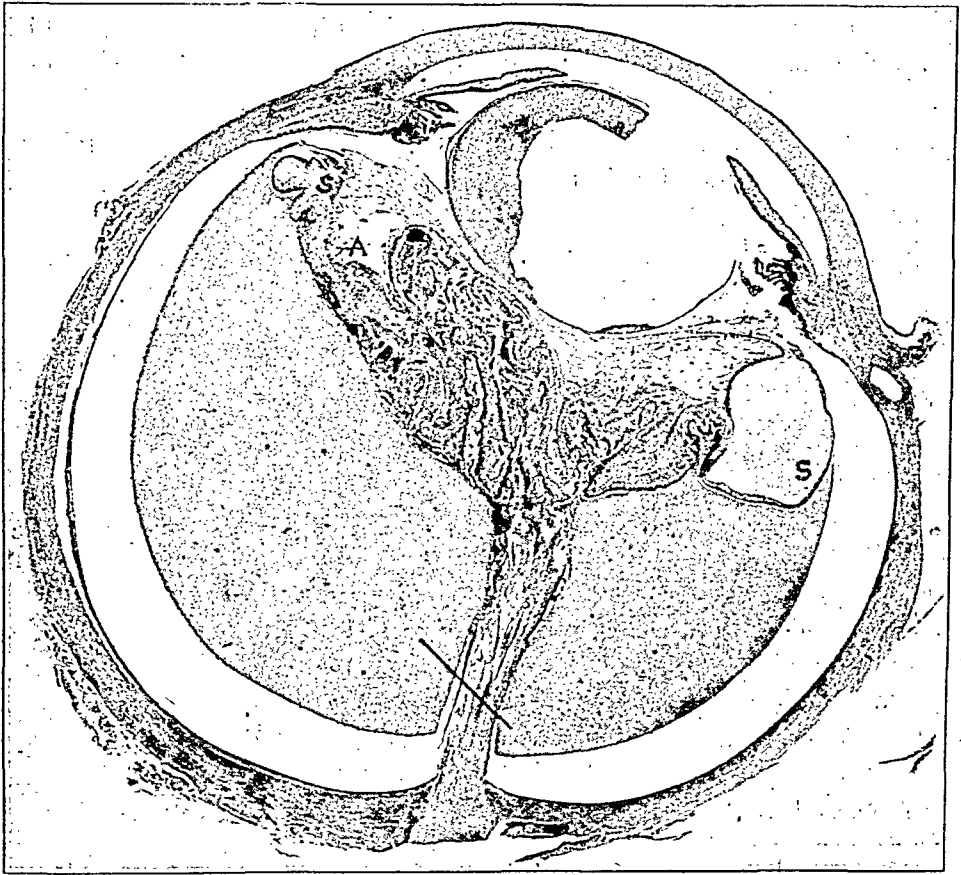


Fig. 1 (case 1).—Right eye. *S* indicates a rudimentary secondary vitreous; *A*, angiomas invading the retina.

Information regarding the maternal history, weight at birth and degree of prematurity could not be obtained. Ten days prior to the first examination the mother had noted a gray reflex from the right pupil.

*Clinical Findings.*—Right Eye: The anterior chamber was extremely shallow. In the nasal half of the globe there was a grayish mass with superficial blood vessels behind the lens. A red reflex was obtained from the temporal side.

6. Reese, A. B.: Persistence and Hyperplasia of Primary Vitreous; Retrolental Fibroplasia: Two Entities, *Arch. Ophth.*, this issue, p. 527.

possibly a persistent dorsal retinal fold. Between the falciform retinal fold and the equatorial region of the lens was a network of thin-walled, tortuous vessels within a delicate scaffolding of connective tissue. Some of these vessels entered the retina (fig. 5), coursing within it for some distance and then returning to the remnants of primary vitreous. The pigment epithelium was normal, except just above the nerve head, where it had proliferated as though stimulated by traction.

In both eyes of this patient there was extensive failure of primary retinal coaptation and of formation of secondary vitreous, and not a true retinal detachment.

CASE 2.—This case illustrates a type of retrolental fibroplasia different from that just described, and apparently the one more frequently encountered. A. L.,

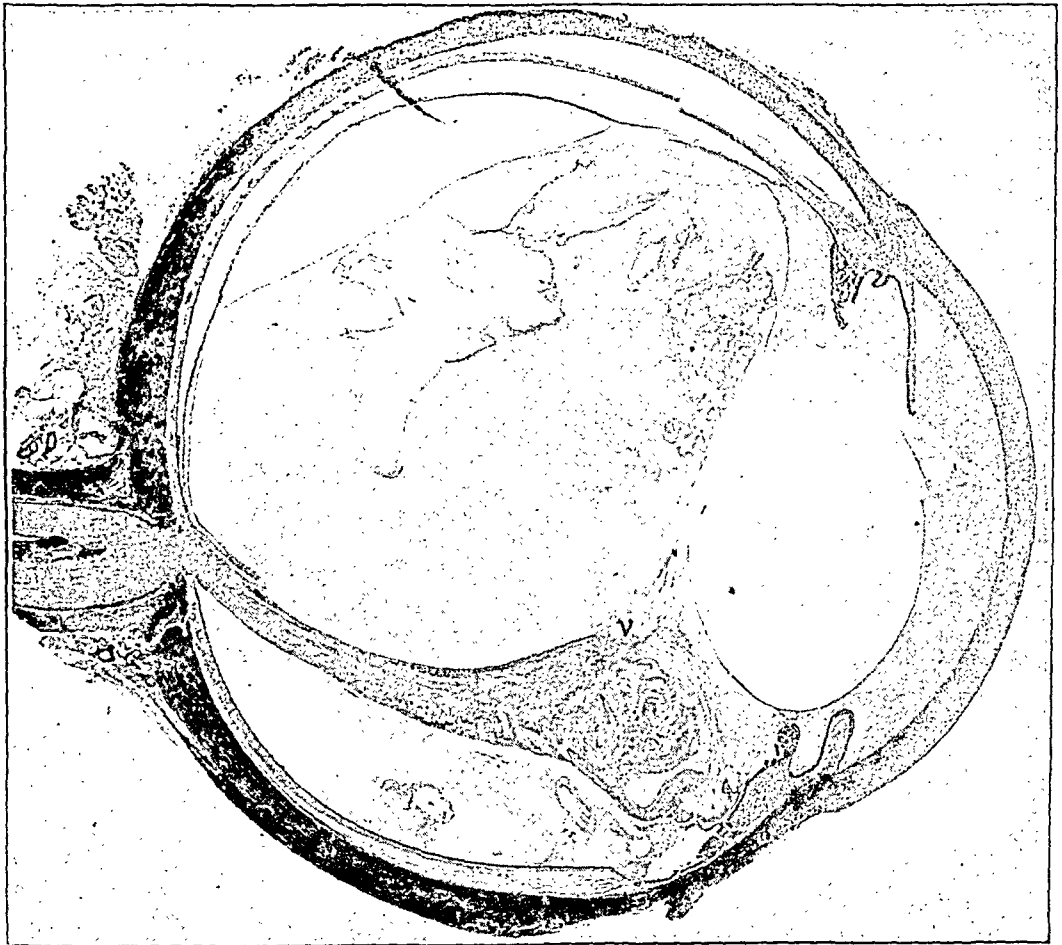


Fig. 4 (case 1).—Left eye, showing falciform retinal fold. *V* indicates vessels in remnant of primary vitreous.

aged 10 months, born six and one-half months prematurely, weighed 22 ounces (624 Gm.) at birth. At the age of 3½ months a white reflex from both pupils was noted by the mother. During the past few weeks the child seemed to have had discomfort in his left eye.

*Clinical Findings.*—Right Eye: The anterior chamber was extremely shallow. Behind the lens, the anteroposterior diameter of which appeared somewhat diminished, there was a grayish white tissue with blood vessels visible on its surface.

Left Eye: The ciliary body was mildly injected. The anterior chamber was extremely shallow, and just nasal to the center the iris was in contact with the

lens were extensive remnants of the primary vitreous, which contained a large number of angiomatous, thin-walled blood vessels. Some of these vessels sent finger-like extensions into the adjacent retina, and at the end of each intraretinal sprout were nodules, consisting of proliferated endothelial cells (figs. 2 and 3). The remnants of primary vitreous contained small, free hemorrhages here and there and at the border of the adjoining rudimentary secondary vitreous there was a wall of fibrous tissue, which represented organization products of hemorrhages. The subretinal space was filled with a homogeneous coagulum. Pigment epithelium and choroid appeared normal.

Left Eye: The bulb measured 19 by 17 by 20 mm. The cornea had a horizontal diameter of 10 mm. The structures of the angle of the chamber were well devel-

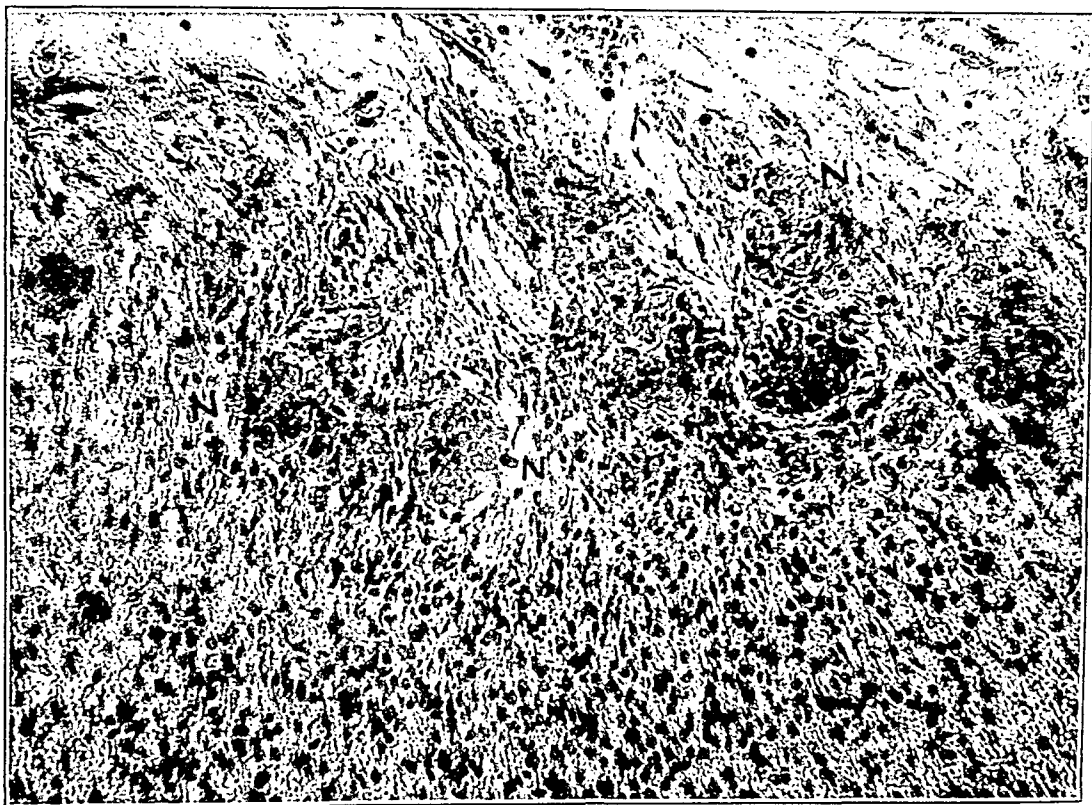


Fig. 3 (case 1).—Right eye: nodules (*N*) of proliferated endothelial cells in focus.

oped, but the angles were obliterated by extensive anterior synechias. The iris was atrophic and covered with a thin fibrous membrane, which had caused a marked ectropion of the pigment epithelium on one side and almost a reduplication of the iris on itself on the other side. The lens measured 4.5 by 6 mm.; the zonular fibers were well developed. The superior and temporal portions of the retina were artificially detached and showed marked dysplasia, consisting of a thin, almost completely glial membrane. The inferior and nasal portions of the retina were folded into a falciform structure (fig. 4), outside of which there was granular coagulum. The optic nerve head was drawn toward this retinal fold and there was considerable supertraction of the opposite part of the retina, or



Fig. 6 (case 2).—Fibrous tissue (*F*) between retina and equator of lens, containing many tortuous, partly collapsed blood vessels.

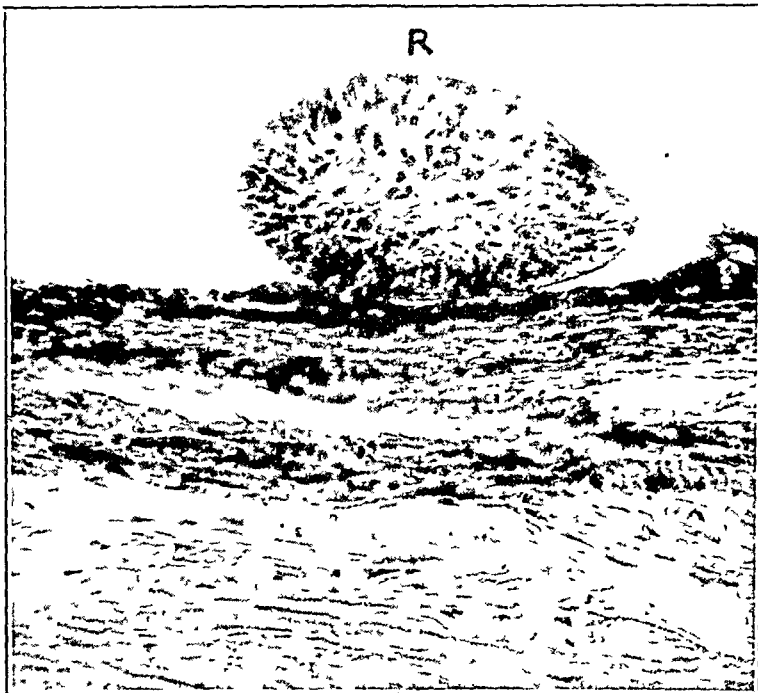


Fig. 7 (case 2).—Torn out piece of retina (*R*) adherent to pigment epithelium

cornea, the surface of which was slightly stippled. Otherwise the picture was similar to that of the right eye. The tactile tension of the left eye seemed increased.

**General Data:** The general physical findings were normal. The weight at the age of 10 months was 11 pounds 7 ounces (5,188 Gm.).

**Course.**—The left eye was removed, because the secondary glaucoma raised the suspicion of a retinoblastoma.

**Histologic Study.**—Left Eye: The sagittal diameter was 17 mm., the frontal 17 mm. and the vertical 18 mm. The cornea measured 8.5 by 9.5 mm. There were

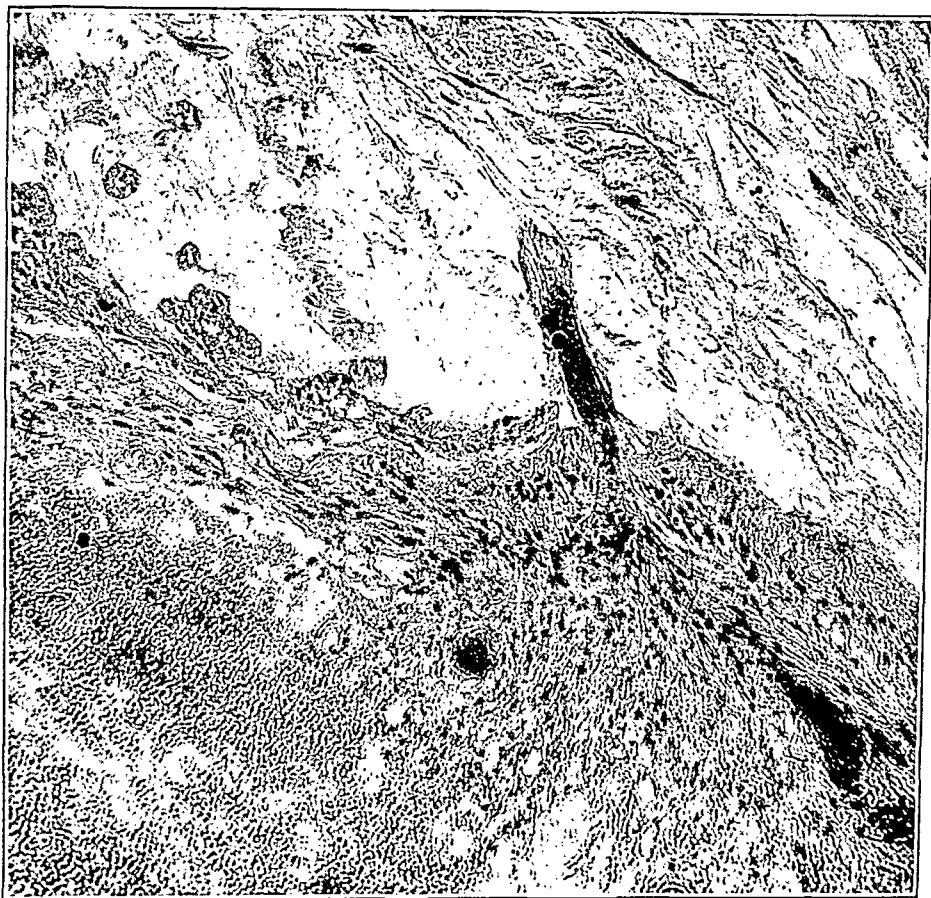


Fig. 5 (case 1).—Left eye: magnification of area at *V* in figure 4, showing blood vessel entering retina from primary vitreous.

short peripheral anterior synechias and below the center of the cornea a more extensive anterior synechia, which had led already to formation of a substance between the cornea and the iris resembling Descemet's membrane. The pupillary borders were adherent to the lens, which had an anteroposterior diameter of 2.5 mm. The iris was greatly atrophied. The ciliary body was drawn inward; some of its processes were elongated, and the pigmented and nonpigmented epithelium showed excessive proliferation. There was an axial detachment of the retina (fig. 6). The retina was degenerated and formed many pseudorosettes. It was suffused with blood, especially behind the temporal equatorial region of the

torial region of the lens and near the base of the vitreous begin to exert traction on the retina and lead to its detachment.

A good example of a disease which is based on a congenital anomaly but may remain latent for two or three decades is von Hippel-Lindau angiomatosis. The angioblastomas in the retina and the central nervous system which characterize this disease have their inception, according to Lindau, during the third month of fetal life but do not become manifest until late in adult life.

Once the full picture of retrolental fibroplasia has developed, hemangiomas may become lost within the shrinking fibrous tissue and the masses of proliferated pigmented and nonpigmented epithelial cells of the ciliary body, and in histologic preparations of old cases of retrolental fibroplasia they may be difficult to demonstrate.

In this connection, a recent clinical observation may be of interest.

CASE 3.7—M. R., a 6½ month old infant, born six and one-half months prematurely, had a weight at birth of 2½ pounds (1,134 Gm.). Bilateral retrolental fibroplasia was first noted at the age of 3 months. At the same time a reddish area was observed in the left pupil. At the time of the first examination, at the age of 6½ months, there was behind the posterior pole of the lens a well defined, red area with a knobby surface, which was connected with a large blood vessel and had the appearance of a hemangioma, rather than of a hemorrhage present for three months (fig. 8).

If further studies should prove beyond doubt the primary role of hemangiomas, regardless of their cause, in the pathogenesis of retrolental fibroplasia, an origin which is strongly suggested by the histologic material presented by Reese and myself and by some clinical observations (Reese,<sup>6</sup> Ingalls<sup>8</sup>), then Reese's modified roentgen therapy could be employed in a preventive manner to the eyes of extremely premature infants of mothers who give histories of uterine bleeding or of other systemic disturbances during gestation.

109 North Wabash Avenue (2).

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7. This patient was seen in consultation with Dr. Kenneth Roper.

8. Ingalls, T. H.: Epidemiology of Encephalo-Ophthalmic Dysplasia, J. A. M. A. **138**:261 (Sept. 25) 1948.



lens. The subretinal coagulum contained masses of cholesterol crystals and fatty granular cells. Between the lens and the retina was a delicate fibrous tissue, which became broader toward the equator of the lens, especially on the temporal side, where it contained a network of thin-walled, partly patent, partly collapsed blood vessels. Some of these vessels were creeping along the inner surface of the retina. Plaques of denser fibrous tissue, surrounded by free hemorrhage, were applied to the surface of the retina in several places. The choroid was shrunk as a result of fixation but appeared normal. There was irregular proliferation of the pigmented epithelium, and in several places torn-out pieces of retina were adherent to its inner surface (fig. 7).

In this case the shreds of retina still adherent to the choroid indicated a true retinal detachment, and not a failure of primary retinal coaptation, as in the first case.

#### COMMENT

Angioblastic overgrowth of the primary vitreous in response to some disturbance as yet unknown—anoxia was suggested by Ingalls

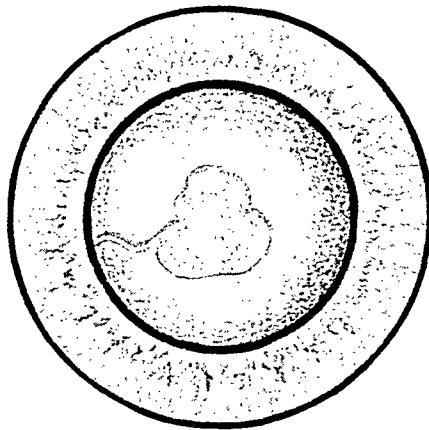


Fig. 8 (case 3).—Large blood vessel behind lens connected with knobby, reddish area with appearance of a hemangioma.

—may occur at any stage of gestation after formation of the primary vitreous has started. Depending on this time element, the retina may be involved in various ways, and different histologic pictures of retrolental fibroplasia may be produced.

Occurring in the primary vitreous early, before the 13 mm. stage, as in the eyes in the first case discussed here, these angiomas, by invading the retina, may more or less extensively prevent primary coaptation of the retina and formation of the secondary vitreous. No inflammatory lesion need to be assumed to explain the firm attachment between primary vitreous and retina in these cases.

Angiomas forming within remnants of the primary vitreous at a later stage need not interfere with normal development of the eye and might remain latent until some time after the premature birth, when hemorrhages and their organization products behind the equa-

two or more of the tests used indicated divergence insufficiency. Not included were 175 others for whom one measurement indicated the defect—usually the reading in the prism-screen test or values for lateral vergences at near points. These patients, although many of them offered the same complaints (headaches, dizziness, ocular fatigue, blurred vision for distance) as did the others, were excluded on the grounds that the symptoms probably resulted from errors in refraction. Undoubtedly, some of them will show gradual increase in the divergence insufficiency and later will be found to need care for it.

In order to acquire dependable data on the problem, one must be aware of its chief characteristics. Because of the close relation between divergence insufficiency and convergence excess, some confusion has found its way into descriptions of this condition.

Scobee's<sup>2</sup> definition is:

. . . (3) Divergence insufficiency—if there is either exophoria or exotropia, and it is greater at near than at far, there is divergence insufficiency.

This specification appears unnecessarily involved.

Duane<sup>3</sup> defined the deficiency thus:

. . . Weakness of the diverging power, characterized by the following signs:

For Distance.—Esophoria of varying amount . . . by all tests (phorometer, screen and parallax). Associated lateral movements normal. Diverging power very much reduced, the reduction being proportionate to the degree of the the esophoria.

Prism convergence (adduction) normal, or often somewhat deficient. Exercise of the convergence often gives rise to a temporary homonymous diplopia, and the latter may also in some cases . . . occur spontaneously, or be evoked by simply placing a red glass before one eye.

For Near.—Signs, unless the condition is associated with a convergence insufficiency or with a convergence excess, fairly normal.

This statement seems sufficiently clear to admit of its being understood as a practical working formula. Briefly, one might start with the premise of an esophoria for distance that is reduced at the near point and which increases in amount as the distance is lengthened.

Both Duane<sup>3</sup> and White<sup>4</sup> expressed the feeling that great care should be taken in diagnosis of these cases of divergence insufficiency, since in each the defect may be combined with, or may grow out of, an actual convergence excess or convergence insufficiency. They cautioned, further, that care be used to determine that the given patient

2. Scobee,<sup>1</sup> p. 250.

3. Duane, A.: (a) *A New Classification of the Motor Anomalies of the Eye*, *Ann. Ophth. & Otol.* 5:969-1008, 1896; 6:84-122 and 247 and 260, 1897; (b) New York, J. H. Vail & Co., 1897, pp. 83-84.

4. White, J. W.: Unpublished lectures at New York Post-Graduate Medical School and Hospital, 1943.

## DIVERGENCE INSUFFICIENCY AS A PRACTICAL PROBLEM

L. WESTON OAKS, M.D.

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**D**IVERGENCE insufficiency is a definite clinical entity. It exists as a practical problem, irrespective of whether pros or cons dominate the perpetual argument over existence of a divergence center in the brain.

The variety of definitions in the literature suggests some confusion as to the characteristics and nature of the condition. Generally, it is the impression that differences of expression arise largely from a paucity of case studies carried out to reasonable completion. Thus, one writer draws conclusions from use of the Maddox rod and taking of ductions with Risley prisms. Another uses only the findings of prism-screen tests. Another allots more importance to lateral vergences at near points and tries to delegate to them arbitrary "normal" values, by which to be guided.

It seems to matter little whether one considers divergence as an active process presided over by a brain center, located near the nuclei of origin of the abducens nerve, or goes along with Scobee,<sup>1</sup> when he says:

Evidence has been produced (Scobee and Green 1946) which indicates that esophoria and exophoria are not two separate entities but merely varying degrees of the same thing. In the light of this fact, the etiology of esophoria and exophoria should be similar in the sense that etiologic factors playing upon the convergence center might result either in a hypertonic state (esophoria) or a hypotonic state (exophoria).

Two things appear to be important: (1) to recognize that the clinical entity does exist with sufficient frequency to represent an important part of the daily refraction patients, and (2) to see that, if one is to appreciate properly the need for treatment of such a patient, data must be carefully obtained.

Cases of divergence insufficiency are not rare. In an analysis of 2,600 refractions, I found this problem appearing in 129, or nearly 5 per cent. This number included only patients in whose examinations

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Read before Pacific Coast Oto-Ophthalmological Society, Seattle, June 9, 1948.

1. Scobee, R. G.: *The Oculorotary Muscles*, St. Louis, C. V. Mosby Company, 1947, p. 136.

readings at 13 inches (33 cm.). A large number of such observations seem to show that certain textbooks on refraction are in error when they state that the values for convergence at the near point should always be larger than those for divergence at the near point. As a matter of fact, it is easily demonstrated that any patient with such a relation between convergence and divergence has discomfort, growing out of some measure of divergence insufficiency or convergence excess or both. Except in certain cases of myopia, correction of refractive errors alone will not relieve the patient's troublesome symptoms. In the average case of hypermetropia, astigmatism or compound errors, it appears desirable for visual comfort to have the divergence at 33 cm. 25 to 50 per cent greater than the convergence at that distance, although a patient may have visual comfort so long as divergence is not less than the convergence.

Lateral prism vergence at near point is measured with the patient wearing the correction for distance—not with a light for fixation, as in the measurement of ductions, but with a black dot or vertical line on a white card. The patient is instructed to hold the spot or line against breaking, while prism, base out or base in, is gradually increased to bring diplopia.

Scobee<sup>6</sup> stated:

. . . I prefer to use an arbitrary limit of fifteen prism diopters of divergence at the reading distance as "normal." If the patient's prism divergence is not at least fifteen prism diopters, one can be reasonably certain that glasses alone will not relieve the patient's symptoms.

It is common experience in all muscle work that little dependence can be placed in any arbitrary standard one sets up, even as a guide, unless one is fully aware of the weaknesses in its use. There are patients who have a sthenic type of response of the extraocular muscles whose convergence at the reading distance may measure 25 to 30  $\Delta$ . By the same token, their normal prism divergence should be more than that amount, or at least its equivalent. Again, one sees persons whose responses are quite the opposite—whose convergence at 13 inches is 9 to 10  $\Delta$ . For such a return on the convergence, a value of 15  $\Delta$  of prism divergence at the near point would suffice. Both types may have normal balance of the extraocular muscles.

Among tests that are made to establish the diagnosis, but which actually offer only corroborative information, the following were used in all cases: 1. Maddox rod and prism on the phorometer. This test, to determine the amount of esophoria, was perhaps used rather as a matter of habit and could readily have been discarded with little effect on the results. 2. Near point of convergence (PcB) at the base of the eyes. This should normally be 95 mm. or less.<sup>3</sup> Among patients with

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6. Scobee,<sup>1</sup> p. 261.

is not really the victim of a mild or moderate paresis of one or both lateral rectus muscles.

In acquiring data from patients here studied, the tests used were divided into two groups, determinative and corroborative. The following tests were considered of determinative importance:

1. Screen-prism measurements. (*a*) The muscle light was at the usual distances; then, in cases in which divergence insufficiency was suggested, the measurement for distance was repeated at from 500 to 5,000 feet (150 meters to 1.5 kilometers), or farther. One should not be satisfied in using the prism-screen test for possible divergence insufficiency with measurement for distance taken only at 20 feet (6 meters). More information may be acquired with the patient facing a window—or moved out of doors—where an object at 500 to 5,000 feet may be had for him to fix on.<sup>5</sup> When this type of imbalance is present, the esophoria will be increased at the greater distance and much diminished at the near point of 30 cm. (*b*) The same test is next carried out at 50 cm. with the eyes in the six cardinal positions to determine any individual muscle weakness. (*c*) Screen-prism measurements should always be preceded by observation of ocular movements, in order to discover possible lagging in any position. The combination of these three details gives ready and dependable evidence of individual muscle weakness.

2. Prism duction tests for distant and near vision, with both breaking and refusing points recorded with Risley prisms on the phorometer. These duction measurements usually reveal a divergence insufficiency, especially in the recovery of abduction at the near range. While this test has been demonstrated by experience to be dependable in the majority of cases, it is insufficient as a basis for diagnosis, since it is subject to serious limitations, especially in its subjective nature, and in the suppression so often shown by patients with mild or severe muscular imbalances.

Use of the rotary prisms, with lights for targets, invariably brings into play numerous reflections, prism "moons," all of which distract the attention of the uninitiated. In vergence tests with Risley prisms, suppression often poses some difficulty. Among the 2,600 patients in the total group, 576 suppressed to an extent interfering with satisfactory prism duction tests.

3. Lateral prism vergence at the near point (33 cm.). Results of convergence and divergence tests at the near point furnish valuable data in any case of muscular imbalance with binocular vision. About ten years ago I began regularly taking convergence and divergence

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5. White, J. W.: Divergence Insufficiency and Palsy, *New York State J. Med.* 47:63-65 (Jan. 1) 1947.

insufficiency and disturbance of vertically acting muscles,<sup>8</sup> hyperphoria of 1  $\Delta$  or more occurred in only 19 of the series. The ages in these cases ranged from 6 to 70 years, with no significant age grouping, except that four fifths of the patients were under 40 years of age. This is not greatly at variance with the percentage of ophthalmic examinations done which fall in that age group.

By analogy, it is only reasonable to consider that divergence insufficiency is no more properly a strange interloper than is convergence insufficiency, convergence excess or divergence excess. The same influences that operate for or against the occurrence of one type may be just as potentially effective in producing another.

Besides the great complexity of the mechanism involved, the very nature of neuromuscular function, especially under stress, favors troublesome combinations. Predication of serious disease of the brain is no more necessary to account for insufficiency of the divergence function or faculty than to account for other insufficiencies or excesses.

In the symptomatology, headache plays a prominent role. In 65 of the 129 cases it was the chief complaint. Next came ocular fatigue, complained of with both near work and distant use of the visual apparatus. Occasional diplopia, nausea, dizziness and blurring of vision—especially for distance, but also for near vision—were encountered. Panoramic headaches, train and car sickness were mentioned by White.<sup>4</sup> Nervous instability was included by Prangen and Koch.<sup>9</sup>

Bruce<sup>8</sup> noted palsy of the lateral rectus muscles late in these cases, indicating that in some the condition is steadily progressive toward that ultimate goal. White<sup>4</sup> stated that some patients require repeated surgical procedures at irregular intervals over the years to maintain visual efficiency. Undoubtedly, these patients represent the severest form, just as one sees patients with convergence insufficiency that is equally difficult to deal with.

Treatment of divergence insufficiency must meet the same general requirements as treatment of other disturbances of vergence integrity—satisfaction of the needs of each individual problem on its merits. The patients should be instructed not to sit far back at the theater, but to locate themselves about fifteen to twenty rows from the front. Beyond some such point, their discomfort will increase with their distance from the screen. For those with presbyopia among them, the reading addition should be attended to, since some patients will be more comfortable in reading at less than 15 inches (33 cm.). In a few cases, with mild hypermetropia, the addition of a  $+ \frac{1}{4}$  to  $+ \frac{1}{2}$  D. sphere (depending on the patient's comfort) to the correction for each eye will be accepted and will give relief from milder symptoms.

\* 8. Bruce, G. M.: Ocular Divergence, *Arch. Ophth.* **13**:639 (April) 1935.

9. Prangen, de H., and Koch, F. L. P.: Divergence Insufficiency, *Am. J. Ophth.* **21**:510 (May) 1938.

divergence insufficiency here covered, the measurements for near point of convergence averaged about the same as they did for the whole group. This is in accord with Duane's statement<sup>3</sup> that the near point of convergence is normal. 3. Interpupillary distance. One might expect this measurement to be short in such cases if there were a close association, in anatomic setup, between divergence insufficiency and convergence excess. Among these patients, 29 had an interpupillary distance of less than 60 mm. The majority of them had between 60 and 65 mm., and 22 showed measurements between 65 and 75 mm.

In diagnosis of muscle problems, it is vital to keep in mind the following points: (a) Theoretic and mathematically calculated arbitrary values will lead one into error, both in estimating a patient's needs and in one's performance of surgical corrections on such a basis, and (b) any formula one sets up by which to evaluate abnormalities must be broad and flexible, so that there is no temptation to crowd an individual case into an established pattern. No system of values one might arrive at will ever be an acceptable substitute for careful study of each patient's problem on its own merits. There is probably no part of medical practice in which this is more true than in the study and treatment of heterophorias and squints.

The cause of divergence insufficiency has been most commonly identified with progressive convergence excess.<sup>7</sup> Duane<sup>7b</sup> and Fuchs<sup>7c</sup> each considered it both primary and secondary, usually the latter. Fuchs stated that about the only example of primary divergence insufficiency was the divergence palsy of supranuclear origin.

Duane<sup>7b</sup> stated:

Uncomplicated idiopathic divergence-insufficiency is comparatively rare, and, moreover, some of the cases that would seem to fall into this category are probably either really secondary to some disorder of the vertical muscles (elevators or depressors), or are examples of a spurious divergence insufficiency, i.e., of a condition in which there is actual weakness of the externi themselves, either natural or produced by operation. In cases of the latter kind the divergence is indeed weak, but the power of making lateral movements is also lessened, and hence these cases do not come fairly under the head of a simple impairment of diverging function.

Complicated idiopathic divergence-insufficiency is more common. In these cases there is either a convergence-insufficiency which has developed simultaneously with the disorder of divergence, or there is a convergence-excess which is the result of the latter.

Of the 129 cases in the present series, signs of convergence excess were present in only 21. As to the frequent association of divergence

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7. (a) Scobee.<sup>6</sup> (b) Duane.<sup>3</sup> (c) Fuchs, E.: *Fuchs's Text-Book of Ophthalmology*, authorized translation from the twelfth, revised and greatly enlarged German edition, with numerous additions, by A. Duane, ed. 5, Philadelphia, J. B. Lippincott Company, 1917, p. 781.

Patients with divergence insufficiency which is not of sufficient severity to demand surgical intervention should be given the benefit of orthoptic care for a few weeks. Such patients are much slower in response than are patients with convergence insufficiency. Two treatments in each of six weeks may be necessary before any real benefit is apparent. By the end of such a period it should be possible at least to say whether the training offers a chance of helping the patient. For some the sessions must be continued for about three months to insure comfort and easy use of the eyes. A few patients will experience recurrence and may require a second series of treatments, but most of them appear to establish better visual habits and to be permanently relieved.

Patients who will require surgical treatment, and who have no prospect of help from orthoptic training, may usually be recognized within the first three weeks of their treatment. Operation is perhaps best done first on the nondominant eye. White<sup>4</sup> has called attention to the desirability of not doing too much at one time on such a patient, advising the shortening of one lateral rectus muscle, and then, later, of the other if it becomes necessary.

Certainly, it is unwise, if not disastrous, to attack a medial rectus muscle in a case of this kind when the near point of convergence is not definitely closer than normal. The O'Connor cinch shortening operation serves excellently the needs of such patients. It is simple; it can be repeated if necessary, and it gives immediate results, without prolonged postoperative disability.

#### SUMMARY

Divergence insufficiency is a definite clinical entity. It occurs, in some degree, in more than 10 per cent of all cases of refraction in which there is binocular vision. The condition is characterized by esophoria which is greater for distance than for near vision. The cause is uncertain, but there seems no reason that the condition should not occur from the same causes that produce other imbalances of the horizontally acting muscles. Symptoms include headache (not relieved by correction of refractive errors), ocular fatigue and occasional diplopia, nausea, dizziness, blurring of distant vision and panoramic headache.

Detection and diagnosis are accomplished by use of screen-prism tests, prism duction measurements and lateral vergences tests at the near point. The relation of convergence and divergence at the near point are found not to conform to statements in some textbooks. Treatment is best accomplished by (1) proper refraction, (2) increase in the plus sphere correction, (3) use of base-out prisms, when accepted, (4) orthoptic training and (5) surgical intervention.



For most patients with myopia of more than 1 D., no treatment, except for proper refraction and correction, will be required, unless the condition is pronounced and accompanied with considerable headache. This fact appears to be related in some way to the lower degree of tonus in convergence function present with myopia.

In the application of glasses to the correction of divergence insufficiency, one must consider also the use of base-out prisms. These have been both praised<sup>8</sup> and condemned.<sup>9</sup> Duane<sup>10</sup> stated:

The constant wearing of prisms, base out, is in most cases a dangerous expedient, as tending to cause disuse and a consequent further enfeeblement of the abduction power.

It is true that many such patients cannot wear base-out prisms with any degree of ease, but there are others who accept them gratefully and are relieved of discomfort. They wear the same glasses for near work without any apparent disadvantage. I have yet to see the first of the patients show any progression of his imbalance with wearing base-out prisms. Several have improved with such care to the point where the prisms were removed without further symptoms being experienced.

As previously stated, some of these patients, with approximately the same degree of trouble as others who are benefited, cannot wear the prisms or are not made comfortable by their application. So far as I know, there is no way by which one may determine to which group a given patient belongs except by applying base-out prisms in a trial frame and having the patient read with them for a time. One may begin with 1 D. prisms or  $\frac{1}{2}$  D. prisms, depending on the findings, and then increase or decrease the strength, as the case may be, until a comfortable level is found or it is discovered that no combination increases the ease of reading. Theoretically, such determination should be made for distant vision, but in actual practice, the prism the patient accepts at the near point gives relief for distance as well.

Important as well in the scheme of therapy is orthoptic training. This, too, has suffered both condemnation and commendation. Again, it is probably a matter of proper determination as to which measure is suitable for which patient. Orthoptic training, properly carried out, can be, and has been, of great help to many of these persons.

Undoubtedly, those persons who are rapidly benefited by base-in training were victims of a state of unsteady coordination of the horizontally acting rectus muscles. Clinically, this reveals itself in frequent spasms of muscles while prism ductions are being taken. Often successive trials of the same test give widely disparate results.

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10. Duane,<sup>3b</sup> pp. 85-86.



HERMANN LUDWIG FERDINAND von HELMHOLTZ  
1821-1894

# AN EARLY PHOTOGRAPH OF VON HELMHOLTZ WITH EXPLANATORY LETTER

JOSEPH C. AUB, M.D.

Professor of Research Medicine, Harvard Medical School  
BOSTON

The accompanying letter was written by Prof. Ernst von Brücke a few months before his death.<sup>1</sup> He had been professor of physiology at Innsbruck before coming to Boston.

Boston, Dec. 22, 1940

My dear Dr. Aub:

Ninety-four years ago, in 1846, my grandfather studied the reflection of light from the background of the human eye. It was this work that stimulated Brücke's friend, von Helmholtz, to invent the ophthalmoscope. My grandfather was the first one on whom von Helmholtz tried his instrument and the first person in whom he saw the background of the living eye.

These facts came back to me when you inspected my own retina, and I thought you might be interested in an old (so far as I know unpublished) daguerreotype of von Helmholtz (about 1848) which he gave to my grandfather. I should be happy if you would do me the favor of accepting it as a small token of sincere gratitude.

With very best wishes for Xmas and for a happy new year,

As ever yours,

E. Brücke.

The daguerreotype has apparently not previously been published, although it obviously was taken the same day as the one from the collection of Prof. Dr. Claude du Bois-Reymond, dated March 23, 1848, and published in Koenigsberger's life of von Helmholtz<sup>2</sup> in 1903. The picture thus was made one hundred years ago.

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1. It is not generally recognized that Brücke, referred to in the letter, came near to being the discoverer of the ophthalmoscope. As quoted in Sigerist's "The Great Doctors," von Helmholtz stated: "I had to explain to my pupils the theory of the retinal reflex, which originated with Brücke. Brücke only just failed to discover the ophthalmoscope. He failed because he had not asked himself to what optical image the rays reflected from the illuminated eye belong. For his purposes, at the time, this question was superfluous. Had he asked it, he would have found it just as easy as I did to answer it, and the ophthalmoscope would have come into existence earlier than it did . . . . At first I found it difficult to use. Had it not been for my firm theoretical conviction that it would be possible to see the fundus, I might not have persevered. But after about a week I was the first who ever succeeded in getting a clear view of the living human retina."

2. Koenigsberger, L.: Hermann von Helmholtz, Braunschweig, F. Vieweg & Sohn, 1903.

intoxication with quinoline. Basile<sup>6a</sup> observed opacities in the cortex of the lens of rabbits after repeated daily peroral administration of 0.2 to 0.4 cc. of decalol or tetralol; the changes in the lens were seen between eleven days and four weeks after onset of treatment. Chorio-retinal lesions occurred, too.

In the experiments to be reported here, several chemical derivatives of naphthalene were found to be cataractogenic in rats. Although these



Fig. 1.—Optical section of the anterior segment of the eye of a rat fed a diet containing 2 per cent  $\beta$ -tetralol for two and one-half weeks.

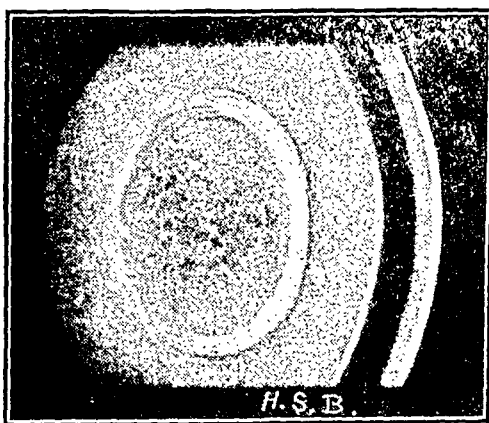


Fig. 2.—Optical section of the anterior segment of the eye of a rat fed a diet containing 2 per cent  $\beta$ -tetralol for four weeks.

experiments do not provide any positive evidence of the mechanism of production of this cataract, they do show that other compounds are more potent as cataractogenic agents than naphthalene. A brief report of the toxic effects of  $\beta$ -tetralol (1,2,3,4-tetrahydro- $\beta$ -naphthol),

6a. Basile, G.: Sull azione di alcuni prodotti di idrogenazione della naftalina (tatalina e dalina) sul cristallino e membrane profonde oculari del coniglio, Boll. d'ocul. 18:951-957, 1939.

# PRODUCTION OF CATARACT IN RATS BY BETA-TETRALOL AND OTHER DERIVATIVES OF NAPHTHALENE

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AND

WILHELM H. BUSCHKE, M.D.  
BALTIMORE

SINCE Bouchard's<sup>1</sup> discovery in 1886 that naphthalene produced cataract in rabbits, a large number of experimental papers have been published on the subject. Relatively few authors, however, have attempted to approach the mechanism of this production of cataract by studying the cataractogenic properties of chemically related substances. Kolinski<sup>2</sup> failed to produce cataract with nitronaphthalene,  $\beta$ -naphthol and anthracene. Salfner<sup>3</sup> had negative results with 1,5-dioxynaphthalene, 2,3-dioxynaphthalene and 2,7-dioxynaphthalene. He found the cataractogenic properties of naphthalene greatly enhanced by phthalic acid; however, control experiments with other agents which likewise produced renal damage led him to conclude that the effect was a result of damage to the kidney, producing a delayed excretion of naphthalene or a toxic derivative. Igersheimer and Ruben<sup>4</sup> reported negative results with both  $\alpha$ - and  $\beta$ -naphthol, while van der Hoeve<sup>5</sup> produced cataracts in rabbits with  $\beta$ -naphthol. Jess<sup>6</sup> observed occasional fine reversible clefts and opacities in the lens in cases of severe

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From the Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C., and the Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine.

1. Bouchard, A.: Production artificielle de la cataracte, *Rev. gén. d'opht.*, 1886, p. 370.

2. Kolinski, J.: Zur Lehre von der Wirkung des Naphthalins auf des Auge, und über den sogenannten Naphthalinstar, *Arch. f. Ophth.* **35**:25-51, 1889.

3. Salfner, O.: Zur Pathogenese des Naphthalinstars, *Arch. f. Ophth.* **59**: 520-552, 1904.

4. Igersheimer, J., and Ruben, L.: Zur Morphologie und Pathogenese der Naphthalinveränderungen des Auges, *Arch. f. Ophth.* **74**:467-488, 1910.

5. van der Hoeve, J.: Ueber die schädliche Einwirkung des Beta-Naphthols in therapeutischen Dosen auf des menschliche Auge, *Arch. f. Ophth.* **53**:74-78, 1901.

6. Jess, A., in Schieck, F., and Brückner, A.: *Kurzes Handbuch der Ophthalmologie*, Berlin, Julius Springer, 1930, vol 5, p. 270.

slit lamp (fig. 2), and occasionally the deep suture lines were slightly opaque; both the superficial cortex and the nucleus, however, remained clear. At this and at later stages, on examination with the ophthalmoscope, one could see a "lens in lente" with the fundus still visible even in the axial region (fig. 3). At the end of three and one-half months a second shell had formed in the cortex, the deeper shell now being thicker and yellow in appearance (fig. 4). At this stage the fundus still was visible, in spite of the presence of the double ring opacity, but appeared somewhat blurred.

In some rats the eyes were examined four months after discontinuation of the diet containing  $\beta$ -tetralol, which previously had been administered for two months. In these rats the clear cortical layer outside the perinuclear opaque shell was decidedly thicker than that in the rats which had been observed at one-half week intervals continually for one month while receiving the diet containing  $\beta$ -tetralol. This indi-

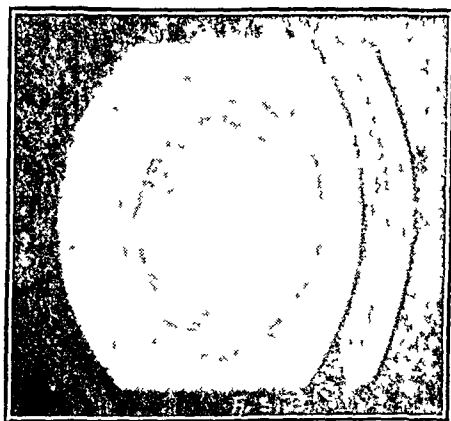


Fig. 4.—Optical section of the anterior segment of the eye of a rat fed a diet containing 2 per cent  $\beta$ -tetralol for three and one-half months.

cates that no permanent irreversible damage to the lenticular epithelium was produced even by prolonged  $\beta$ -tetralol poisoning. The epithelium of the lens appeared to continue to proliferate (or to resume proliferation) and to appose healthy lens cortex after discontinuation of the drug. In these rats the nuclear suture lines were sometimes either opaque or somewhat gaping. Lenses removed from rats killed after receiving the experimental diet about a month showed a brownish nucleus, which had a harder, drier and more brittle consistency than that of normal animals.

All these changes are essentially identical with those described by Goldmann<sup>9</sup> for rats fed naphthalene. No other ocular changes were noticed; in particular, there was no pathologic vascularization of the cornea.

9. Goldmann, H.: Experimentelle Supranuclærkatarakt und Kernsklerose, Klin. Monatsbl. f. Augenh. **83**:433-438, 1929.

which was proposed as an insect repellent,<sup>7</sup> has been made by one of us.<sup>8</sup> In the study of  $\beta$ -tetralol, over 200 rats were used, with dosage levels of 0.125, 0.25, 0.5, 1 and 2 per cent in the diet. Both weanling and adult rats were employed.

#### EYES OF RATS FED $\beta$ -TETRALOL

Cataracts were observed in all rats with dosage levels of 0.25 per cent or more in the diet. Both the severity and the time of development of the cataracts depended on the dosage level. Cataracts could be seen grossly within three weeks in all rats given diets containing 1 and 2 per cent  $\beta$ -tetralol. In order to see the cataracts in the rats with lower dosage levels and at earlier stages, the slit lamp had to be used. The rats given the diet containing 0.125 per cent  $\beta$ -tetralol were observed for six months, without the development of cataracts.

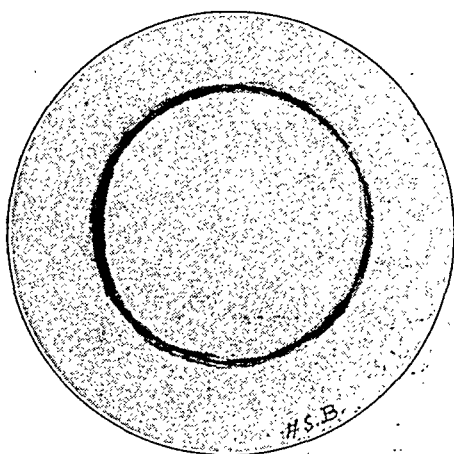


Fig. 3.—Diascopic appearance of the lens of a rat fed a diet containing 2 per cent  $\beta$ -tetralol ("lens in lente") for four weeks.

The eyes of the rats were examined in mydriasis with the slit lamp and the ophthalmoscope at intervals of one-half week during the first month after institution of the diet, and later at longer intervals.

Changes in the lenses visible with the slit lamp began to appear regularly between two and two and one-half weeks after beginning ingestion of the diet containing 2 per cent  $\beta$ -tetralol. These manifestations began with a very fine, sometimes incomplete, supranuclear haziness, which soon developed into a complete perinuclear layer showing an increased Tyndall phenomenon (fig. 1). A complete thin perinuclear shell was regularly present three weeks after institution of the diet. After four weeks this shell layer appeared somewhat denser with the

7. Jachowski, L. A., and Pijoan, M.: Two New Effective Insect Repellents NMRI-201 and NMRI-448, *Science* **104**:266-269, 1946.

8. Fitzhugh, O. G.: Production of Cataracts in Rats with Beta-Tetralol. *Federation Proc.* **5**:178, 1946.

amine. A 2 per cent concentration of each substance was incorporated in the diet and fed to 5 weanling rats for at least two months. These sub-

*Relative Cataractogenic Property of Derivatives of Naphthalene—Continued*

Name	Structural Formula	Estimated Cataractogenic Potency Compared to That of Naphthalene, Expressed as 1
2-methoxy-1, 2, 3, 4-tetrahydronaphthalene		1
$\alpha$ -tetralol		0
Trans- $\beta$ -decalol		0
Tetrahydronaphthalene		0
Decahydronaphthalene		0

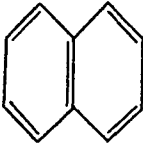
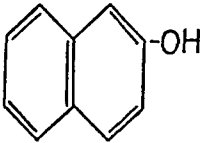
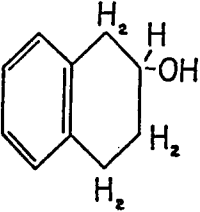
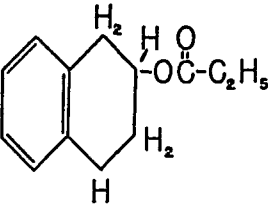
stances were compared as cataractogenic agents both with  $\beta$ -tetralol and with naphthalene (table).



## EYES OF RATS TREATED WITH OTHER DERIVATIVES OF NAPHTHALENE

In addition to the  $\beta$ -tetralol, the following derivatives of naphthalene were studied for their possible cataractogenic property: 1,2,3,4-tetrahydro-2-naphthyl propionate, 2-methoxy-1,2,3,4-tetrahydronaphthalene,

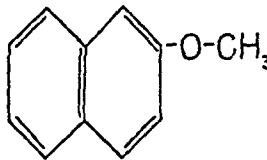
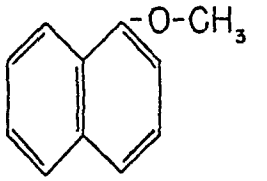
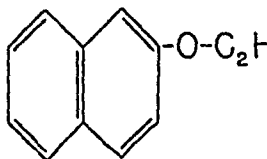
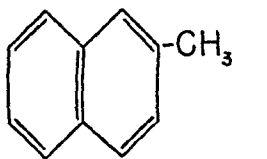
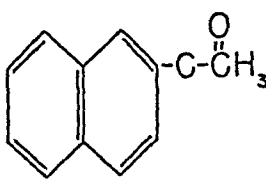
*Relative Cataractogenic Property of Derivatives of Naphthalene*

Name	Structural Formula	Estimated Cataractogenic Potency Compared to That of Naphthalene, Expressed as 1
Naphthalene		1
$\beta$ -naphthol		1
$\beta$ -tetralol		4
1, 2, 3, 4-tetrahydro-2-naphthylpropionate		4

$\alpha$ -tetralol,  $\beta$ -naphthol, trans- $\beta$ -decalol (decahydronaphthol), tétrahydronaphthalene, decahydronaphthalene,  $\beta$ -naphthylacetate,  $\alpha$ -naphthylacetate,  $\beta$ -naphthylsalicylate,  $\beta$ -naphthylbenzoate,  $\alpha$ -naphthylbenzoate,  $\beta$ -naphthylmethyl ether,  $\alpha$ -naphthylmethyl ether,  $\beta$ -naphthylethyl ether,  $\beta$ -methylnaphthalene,  $\beta$ -acetonaphthone, naphthalene- $\beta$ -sulfonylchloride,  $\beta$ -naphthoic acid,  $\alpha$ -naphthoic acid,  $\beta$ -naphthylamine and  $\alpha$ -naphthyl-

took much longer to produce the same degree of cataract formation and were closely comparable to naphthalene as cataractogenic

*Relative Cataractogenic Property of Derivatives of Naphthalene—Continued*

Name	Structural Formula	Estimated Cataractogenic Potency Compared to That of Naphthalene, Expressed as 1
$\beta$ -naphthylmethyl ether		1
$\alpha$ -naphthylmethyl ether		0
$\beta$ -naphthylethyl ether		1
$\beta$ -methylnaphthylene		0
$\beta$ -acetoneaphthone		0

agents. All the cataracts appeared to be of the same type. The eyes of the rats which had been fed 1,2,3,4-tetrahydro-2-naphthylpropionate were examined with an ophthalmoscope. They showed changes in the lens similar to those described for the rats treated with  $\beta$ -tetralol.

1,2,3,4-tetrahydro-2-naphthylpropionate, 2-methoxy-1,2,3,4-tetrahydronaphthalene,  $\beta$ -naphthol,  $\beta$ -naphthylsalicylate,  $\beta$ -naphthylmethyl

•Relative Cataractogenic Property of Derivatives of Naphthalene—Continued

Name	Structural Formula	Estimated Cataractogenic Patency Compared to That of Naphthalene, Expressed as 1
$\beta$ -naphthylacetate		0
$\alpha$ -naphthylacetate		0
$\beta$ -naphthylsalicylate		4
$\beta$ -naphthylbenzoate		0
$\alpha$ -naphthylbenzoate		0

ether and  $\beta$ -naphthylethyl ether produced cataracts in all rats. The 1,2,3,4-tetrahydro-2-naphthylpropionate and the  $\beta$ -naphthylsalicylate produced cataracts as quickly as the  $\beta$ -tetralol. The other substances

by binding essential sulfhydryl groups in the lens. Experiments with 2, 3-dimercaptopropanol (BAL), methionine, cystine and high protein diets did not support this theory. A large number of rats were treated with BAL, both by local application to the eye and by parenteral injection. The dosage levels of BAL were 3 mg. per kilogram of body weight given twice weekly for the parenteral injections and 0.01 cc. of a 5 per cent ointment placed in each eye daily for the local applications. The treatment with BAL was continued until cataracts appeared. In all instances the treatment with BAL had no effect either on the rate of development or on the severity of the cataracts. Neither a 50 per cent protein diet nor the addition of methionine equivalent to 100 mg. daily to the diet of each rat had any effect on the production of cataracts in rats fed 2 per cent  $\beta$ -tetralol. After a diet containing 1 per cent cystine had shown no effect on the production of cataract with 2 per cent  $\beta$ -tetralol, a diet containing 3 per cent cystine and 0.2 per cent  $\beta$ -tetralol was fed to rats. Cataracts occurred in these rats in the same length of time that they appeared in control rats, without the added cystine.

In other experiments, 0.03 per cent riboflavin and 2 per cent ascorbic acid in the diet failed to have any effect on the production of cataracts with  $\beta$ -tetralol.

#### COMMENT

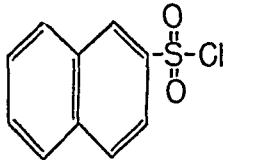
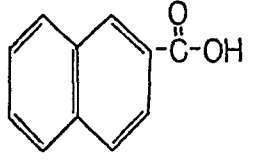
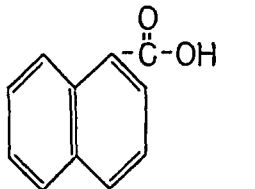
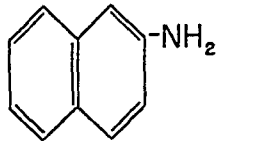
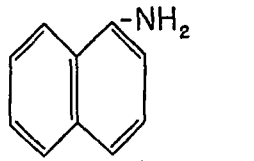
Although the changes in the lens produced by feeding  $\beta$ -tetralol and related naphthalene derivatives are essentially identical with those described in *naphthalene poisoning in rats*, the difference in potency of these substances as cataractogenic agents is considerable.  $\beta$ -tetralol, 1,2,3,4-tetrahydro-2-naphthylpropionate, and  $\beta$ -naphthylsalicylate produced decided cataracts in three weeks, whereas similar doses of  $\beta$ -naphthol and naphthalene in the diet produced only slight cataracts in two months. Parenteral administration of solutions of  $\beta$ -tetralol,  $\beta$ -naphthol and naphthalene in peanut oil at similar dosage levels indicated that by this route also  $\beta$ -tetralol was more potent than the other substances. A single injection of tetralol equivalent to the amount received daily in the diet produced death within a few minutes. One-fourth this amount injected daily produced cataract in three weeks. Similar parenteral doses of  $\beta$ -naphthol and naphthalene had no effect. With an increase in the amount either of  $\beta$ -naphthol or of naphthalene to twice the dose of  $\beta$ -tetralol which produced pronounced cataracts, slight cataracts occurred.

These experiments indicate that derivatives of naphthalene in which an oxygen atom is attached to the  $\beta$  carbon atom may produce cataracts in rats. In the case of trans- $\beta$ -decalol, both the naphthalene rings are completely saturated, and this fact may account for the lack of any cataractogenic property. Apparently, the  $\beta$ -naphthylbenzoate and the  $\beta$ -naphthylacetate are not metabolized like the  $\beta$ -naphthylsalicylate, or

ATTEMPT TO PREVENT THE FORMATION OF  $\beta$ -TETRALOL CATARACT

Since naphthalene is excreted in rats as a mercapturic acid,<sup>10</sup> it appeared possible that the derivatives of naphthalene produced cataract

*Relative Cataractogenic Property of Derivatives of Naphthalene—Continued*

Name	Structural Formula	Estimated Cataractogenic Potency Compared to That of Naphthalene, Expressed as 1
Naphthalene- $\beta$ -sulfonyl chloride		0
$\beta$ -naphthoic acid		0
$\alpha$ -naphthoic acid		0
$\beta$ -naphthylamine		0
$\alpha$ -naphthylamine		0

10. Stekol, J. A.: Studies on Mercapturic Acid Synthesis in Animals: D. The Effect of Naphthalene on the Growth of Rats as Related to Diets of Varying Sulfur Content, *J. Biol. Chem.* **121**:87-91, 1937.

## USE OF ANTIHISTAMINIC DRUGS IN CONTROL OF ATROPINE DERMATITIS AND CONJUNCTIVITIS

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AND

ROBERT D. KIESS, M.D.

ANN ARBOR, MICH.

**P**HARMACEUTICAL chemists have long attempted to produce a satisfactory substitute for atropine sulfate. The desire to synthesize a substitute cycloplegic and mydriatic not related to the atropine series has been furthered by the fact that contact dermatitis and conjunctivitis occasionally develop in patients using atropine in treatment of iridocyclitis. This reaction may reach such serious proportions that it is necessary to discontinue administration of the drug. The management of the allergic manifestations usually requires discontinuation of the atropine, with substitution of homatropine, scopolamine or duboisine and the application of cold wet compresses. These substitute drugs present two disadvantages. First, none of the drugs produces a sufficiently strong cycloplegic or mydriatic action to be effective in the treatment of acute iridocyclitis. Second, the patient who is sensitized to atropine frequently demonstrates hypersensitivity to these substitute drugs, since they too belong to the atropine series.

The absence of an adequate substitute for atropine in the treatment of acute iridocyclitis often makes it imperative that use of the atropine be continued despite its side effects. However, with the advent of the antihistaminic drugs and their proved value in treatment of extrinsic allergic states, there is now available an effective aid in the control of the serious cutaneous and conjunctival manifestations of atropine hypersensitivity.

The earliest characteristic symptom of such hypersensitivity is itching. This is usually accompanied with irritation and photophobia before any of the well known signs of erythema, edema and eczema of the skin of the lids become apparent. An increase in mucous dis-

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From the Department of Ophthalmic Surgery, University of Michigan.

The various doses of the antihistaminic drugs were determined with the advice of J. H. Sheldon, M.D., Chief of the Division of Allergy, Department of Internal Medicine, University of Michigan.

The diphenhydramine (benadryl®) solution used was supplied by Parke, Davis & Company, Detroit; the tripeleennamine (antistin®) solution, by Ciba Pharmaceutical Products, Inc., Lafayette Park, Summit, N. J.

are not absorbed at the same rate. The experiments with the two former substances were continued for eight months without the production of cataract; this fact does not exclude the possibility of the production of cataract with prolonged feeding to rats.

#### SUMMARY

Changes in the lens which were similar to those described in naphthalene poisoning in rats were produced by feeding  $\beta$ -tetralol.

A large number of naphthalene derivatives were studied for their possible cataractogenic property. In addition to  $\beta$ -tetralol, 1,2,3,4-tetrahydro-2-naphthylpropionate and  $\beta$ -naphthylsalicylate were more potent as cataractogenic agents than was either naphthalene or  $\beta$ -naphthol.

By parenteral administration,  $\beta$ -tetralol was more than twice as potent in cataractogenic property as was either  $\beta$ -naphthol or naphthalene.

The treatment of rats with sulfhydryl compounds did not prevent the formation of cataract in rats fed  $\beta$ -tetralol.

The slit lamp drawings were made by Mrs. Annette S. Burgess, Wilmer Ophthalmological Institute.

both eyes for two days. The suggested therapeutic regimen was initiated. "Excellent" relief from symptoms and a "good" response in clinical signs were observed in forty-eight hours.

CASE 5.—S. A., a white man aged 55, with retinal separation in the left eye, had been treated with bed rest and pinhole glasses and mydriasis obtained with use of atropine sulfate (1 per cent) once daily, for preoperative study. After two days of medication with atropine, dermatitis and conjunctivitis of the left eye developed. The treatment suggested for control of atropine sensitivity was initiated, with "excellent" symptomatic relief and "good" response in signs within forty-eight hours. At this time diathermy was performed for correction of the retinal detachment. Two days after operation the atropine dermatitis and the conjunctivitis of the left eye recurred. It was found, however, that the patient had not received his antihistaminic medication after operation, and the treatment was reordered. Within forty-eight hours the relief from symptoms was "excellent" and the decrease in signs was "good." It should be noted that the patient's clinical responses on the two occasions were similar.

CASE 6.—F. G., a white woman aged 67, exhibited atropine dermatitis and conjunctivitis on the fifth day after intracapsular cataract extraction with peripheral iridectomy in the left eye. Atropine sulfate (1 per cent) had been instilled daily in the left eye since the operation. Medication consisted in administration of tripeleonnamine hydrochloride (50 mg.) by mouth four times daily and instillation of antistin® solution (2-[n-phenyl-n-benzyl-aminomethyl]-imidazolin), 0.5 per cent, into the left eye four times daily. Within forty-eight hours the relief from symptoms was "good" and the decrease in signs "fair." There was no further change after ten days of this treatment.

CASE 7.—M. M., a white woman aged 34, exhibited severe atropine dermatitis and conjunctivitis fourteen days after discission for congenital cataract of the right eye. She had been receiving atropine sulfate (1 per cent) daily in the eye operated on. Antistin® was used locally four times a day in 0.5 per cent concentration, with the atropine sulfate.

Observation after four days revealed that the signs and symptoms had considerably increased. Medication was then changed to oral use of tripeleonnamine and local instillation of diphenhydramine, as indicated earlier in the paper. The patient was observed for two weeks while receiving this medication, and both symptomatic relief and decrease in signs remained consistently "poor." All medication was then discontinued, since relief from antihistaminic drugs was not obtained.

CASE 8.—B. T., a white youth aged 19, had sustained severe corneal burns from sodium aluminate. A complicating bilateral iritis was being treated with instillations of atropine sulfate (1 per cent) once daily in each eye. After ten days of atropine therapy, dermatitis and conjunctivitis developed. The suggested therapeutic combination of diphenhydramine and tripeleonnamine was given. After forty-eight hours relief of symptoms was "excellent" and decrease in objective signs "good."

CASE 9.—B. M., a white woman aged 58, exhibited atropine dermatitis and conjunctivitis on the third day after intracapsular cataract extraction with peripheral iridectomy in the left eye. Instillation of atropine sulfate (1 per cent) had been given the night before operation and was continued at the daily dressings. The usual therapy was ordered. Within forty-eight hours "excellent" symptomatic relief and "good" response in clinical signs were obtained. This therapeutic regimen was continued, and an intracapsular cataract extraction with peripheral



charge, together with chemosis and increased hyperemia of the conjunctiva, makes an early appearance. The conjunctiva commonly presents follicular hypertrophy.

The following treatment has given gratifying results in the control of atropine hypersensitivity: (1) general medication, consisting in administration of tripeleennamine hydrochloride (pyribenzamine hydrochloride®; N,N-dimethyl-N'-benzyl-N'-[ $\alpha$ -pyridyl] ethylenediamine hydrochloride), 50 mg. by mouth four times a day: (2) local application of solution of diphenhydramine hydrochloride (benadryl hydrochloride®), 0.5 or 0.25 per cent,<sup>1</sup> four times a day. In all cases atropine sulfate (1 per cent) was continued in order that the mydriasis might be maintained.

This paper presents the reports of treatment in 9 consecutive cases of atropine sensitivity. The results, both objective and subjective, in these cases were evaluated as "excellent," "good," "fair" and "poor."

#### REPORT OF CASES

CASE 1.—J. W., a white man aged 63, exhibited the classic signs and symptoms of atropine dermatitis and conjunctivitis on the third day after intracapsular cataract extraction with peripheral iridectomy in the left eye. He had been receiving instillations of atropine sulfate (1 per cent) once daily in the left eye for five days. His symptoms were intense itching and irritability. Objective signs were pronounced injection of the conjunctival vessels, mild chemosis, eczema, erythema and edema of both lids. The suggested therapeutic regimen was initiated, and within forty-eight hours there was "excellent" relief from the symptoms and the decrease in signs was noted as "good."

This plan of therapy was continued for eleven days, during which time there was little change in the symptoms and signs.

CASE 2.—J. H., a white man aged 65, exhibited the typical signs and symptoms of atropine dermatitis and conjunctivitis on the third day after intracapsular cataract extraction with peripheral iridectomy in the right eye. He had been receiving atropine sulfate (1 per cent) in the right eye daily for four days. Therapy was carried out as outlined. Within forty-eight hours relief from symptoms was recorded as "good" and decrease in signs as "fair."

Treatment was continued for one week, with no essential change.

CASE 3.—C. G., a white man aged 45, exhibited the usual signs and symptoms of atropine dermatitis and conjunctivitis on the fourth day after iridectomy for acute glaucoma. He had been receiving atropine sulfate (1 per cent) once daily for two days in the surgically treated eye. The suggested therapeutic regimen was begun, and within forty-eight hours "excellent" symptomatic relief and a "good" response in clinical signs were observed.

CASE 4.—H. N., a white man aged 53, exhibited atropine dermatitis and conjunctivitis on the fourth day after bilateral iridectomy for glaucoma secondary to uveitis. Atropine sulfate (1 per cent) had been used once daily in

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1. At present, a 0.25 per cent solution of diphenhydramine hydrochloride is being used.

# CHOROIDAL METASTASIS OF A TESTICULAR CHORIONIC EPITHELIOMA

Report of a Case

GEORGE K. KAMBARA, M.D.  
LOS ANGELES

**M**ETASTASIS of chorionic epithelioma to the choroid is rare. Six cases have been reported in the literature, 3 of occurrence in women and 3 in men. Our case is the seventh one to be reported, and the fourth of occurrence in a man.

The first report of a case of chorionic epithelioma with metastasis to the choroid was made by Mulock-Houwer<sup>1</sup> in 1926. A woman had metastases to the choroid, lung, kidneys and intestine three years after an abortion. The uterus was enlarged. The second report, by Slavik<sup>2</sup> in 1933, was the case of a woman aged 50 who had had a supravaginal hysterectomy for hydatidiform mole. She had had an attack of acute glaucoma, for which enucleation was performed. A metastasis was noted in the choroid. Two weeks later the patient died with cerebral metastases. Simidu<sup>3</sup> reported the third case in 1935. A woman aged 31 had chorionic epithelioma of the uterus. She also had malignant glaucoma with pain and blindness, requiring enucleation of the left eye. The typical tumor cells were observed in the choroid. There was associated retinal detachment.

In 1936, MacDonald<sup>4</sup> reported the first occurrence of choroidal metastasis from a testicular chorionic epithelioma. A man aged 28 had noted a slowly increasing mass in the left testicle for eight months. Hemoptysis and epistaxis occurred a few months before the loss of vision. Retinal detachment was seen in the right eye, with an underlying visible mass. Enucleation was performed because of the pain and increased tension. Typical cells of chorionic epithelioma were

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From the Department of Ophthalmology of the University of Wisconsin Medical School, Dr. F. A. Davis, Chairman.

1. Mulock-Houwer, A. W.: Metastasis of Malignant Chorio-Epithelioma, *Klin. Monatsbl. f. Augenh.* **77**:226, 1926.

2. Slavik, B.: Metastasis of Malignant Chorionepithelioma into Choroid, *Časop. lék. česk.* **72**:756, 1933.

3. Simidu, S.: Metastase eines malignen Chorioepithelioms in der Aderhaut, *Acta soc. ophth. jap.* **39**:2023, 1935.

4. MacDonald, A. E.: Choroidal Chorionepithelioma Secondary to Teratoma of Testicle, *Arch. Ophth.* **16**:672 (Oct.) 1936.

iridectomy was performed on the right eye one week after the extraction in the left eye. Postoperative orders were written specifically to continue the systemic administration of tripeleppamine, and diphenhydramine therapy was maintained only for the left eye. There was no change in the clinical findings in the left eye. Two days after cataract extraction was performed on the right eye, atropine dermatitis and conjunctivitis in the surgically treated eye developed, despite the oral administration of tripeleppamine. The patient had been receiving atropine sulfate (1 per cent) daily in the right eye for three days. Instillations of diphenhydramine hydrochloride, in 0.5 per cent solution four times a day, in the right eye was added to the therapeutic regimen. Within forty-eight hours the relief from symptoms was "excellent" and the decrease in signs "good."

#### SUMMARY AND CONCLUSIONS

From these consecutive cases, the following general conclusions may be drawn:

1. Atropine sulfate may be continued after the development of atropine dermatitis and conjunctivitis, since the reaction is controllable by concurrent antihistaminic therapy.

2. Pronounced improvement with antihistaminic treatment was noted within forty-eight hours in 8 of 9 consecutive cases of atropine hypersensitivity.

3. In two thirds of the cases reported, relief from symptoms was "excellent" and the decrease in clinical signs was "good."

4. A combination of local and general antihistaminic therapy proved most effective. This finding was most apparent in a case in which atropine hypersensitivity developed during systemic administration of tripeleppamine alone, while in another case the result was poor when treatment was limited initially to local application of an antihistaminic substance.

5. From this limited series, it would seem that the treatment of choice is a combination of oral administration of tripeleppamine hydrochloride and local use of diphenhydramine hydrochloride. The limitations of instillation of a solution into the conjunctival cul-de-sac in the control of reactions of the skin are obvious. Further studies are being conducted with the application of an ointment containing 2 per cent tripeleppamine hydrochloride to the involved areas of the skin.

University Hospital.

The appetite had been poor for two weeks. He also had nocturia, urinating two or three times during the night. He had noted severe generalized weakness. He had lost 8 pounds (3.6 Kg.) in weight.

The past history was noncontributory. His social and family histories were not remarkable.

On examination the patient appeared well developed and fairly well nourished but in apparent distress. There was pallor of the skin, lips and mucous membranes. The anterior cervical lymph nodes were palpable bilaterally. The trachea was deviated slightly to the left. A large, firm, nodular, movable mass, measuring 3 by 3 cm., was felt under the right breast, and a smaller mass was palpable under the left breast. The expansion of the chest was decreased bilaterally. There was dulness over the right side, with decrease to absence of breath



Fig. 1.—Roentgenogram of the chest, showing multiple nodular metastases to both lungs.

sounds. Rales were heard throughout the chest. The heart and mediastinum were shifted to the left. The pulse rate was 108 per minute, and the blood pressure 114 systolic and 68 diastolic. The abdomen was tense, and the edge of the liver was felt to extend 8 to 10 cm. below the costal margin. The surface of the liver was nodular.

The left testis was enlarged, nodular, tender and firm; it measured 5.5 cm. in diameter. The head of the epididymis appeared unaffected. Two firm, tender nodules were attached to the vas deferens, or spermatic cord, just above the epididymis, one being 0.5 cm. and the other 2 cm. in diameter. The right testis was normal. The prostate gland was slightly enlarged, but very tender.

There were no neurologic signs.

I made an ocular examination on Feb. 18, 1947: Vision was 6/200 in the right eye and 20/15 in the left eye. The extraocular movements were good.

observed in the choroid. Metastases were present in the lung, in subcutaneous tissues of the groin, in the skull, brain, nasopharynx, pleura, diaphragm, liver, gallbladder, intestine and kidneys and in the retroperitoneal tissues. The patient also had signs of associated endocrine changes—linea nigra, female distribution of pubic hair and hypertrophy of the breasts.

Reichling<sup>5</sup> presented a case in 1938 in which the eye was enucleated because of a suspected malignant melanoma of the choroid. However, it was demonstrated later that the growth was a metastasis from a tumor of the right testis. The patient died of generalized metastases within two months. Typical tumor cells were observed in the choroid. This report was not complete.

In 1944 Godtfredsen<sup>6</sup> reported the third case of choroidal metastasis in men and presented a review of the previous cases and the biologic and histopathologic characteristics of the tumor. A youth aged 18 had been aware of increasing swelling of the right side of the scrotum for a year. Two months prior to admission aspiration and injection were carried out for cure of the hydrocele. However, there was no improvement, and later semicastration was performed. The diagnosis of chorionic epithelioma was then made. He later noted impairment of vision, and a choroidal tumor was seen superiorly and temporally in the right eye. His general condition became poor, and he died two weeks after admission. Metastases were observed in the cerebrum (cortex), lungs, liver, pancreas, jejunum and skin. The hypophysis showed none of the changes seen in association with pregnancy.

#### REPORT OF CASE

E. B., a man aged 21, was admitted to the Wisconsin General Hospital on Feb. 17, 1947, with the complaint of pain in the right side of his chest. He had been well until November 1946, when there developed a dry cough which was not associated with a cold. This cough persisted into the latter part of December. He then experienced pleuritic pain in the right side of the chest. He began to raise about one-half cup of bloody sputum a day. He noted at this time that the left testis was considerably larger than the right, but it was not painful.

Ten days prior to his admission the left testis became painful, and his right eye felt swollen and began to water. Shortly afterward he noted blurring of vision, and two days prior to admission he was seen at the Davis and Neff Clinic. A small, well demarcated elevation of the retina was noted above and temporal to the disk. The following day the patient had severe pain on both sides of his chest and was admitted for complete study.

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5. Reichling, W.: Ocular Metastasis of a Chorioneptithelioma, *Arch. Opth.* 19:156 (Jan.) 1938.

6. Godtfredsen, E.: Choroid Metastases in Chorioneptithelioma of the Testicle, *Acta opth.* 22:300, 1944.

The clinical diagnosis was primary neoplasm of the left testis, probably a teratoma or chorionic epithelioma, with metastases to the gastrointestinal tract, to both lung fields, to the right eye and to both breasts.

*Laboratory Studies.*—The urine was normal.

Routine studies of the blood showed 9.8 Gm. of hemoglobin, with 3,160,000 red blood corpuscles per cubic millimeter. The white cell count was 11,100, with 72 per cent polymorphonuclear leukocytes (of which 57 per cent were filamentous and 15 per cent nonfilamentous forms), 25 per cent lymphocytes and 3 per cent monocytes. The sugar and nonprotein nitrogen of the blood were within normal limits. The Wassermann reaction of the blood was negative. The sedimentation rate was increased to 35 mm. in one hour, corrected (Wintrobe).

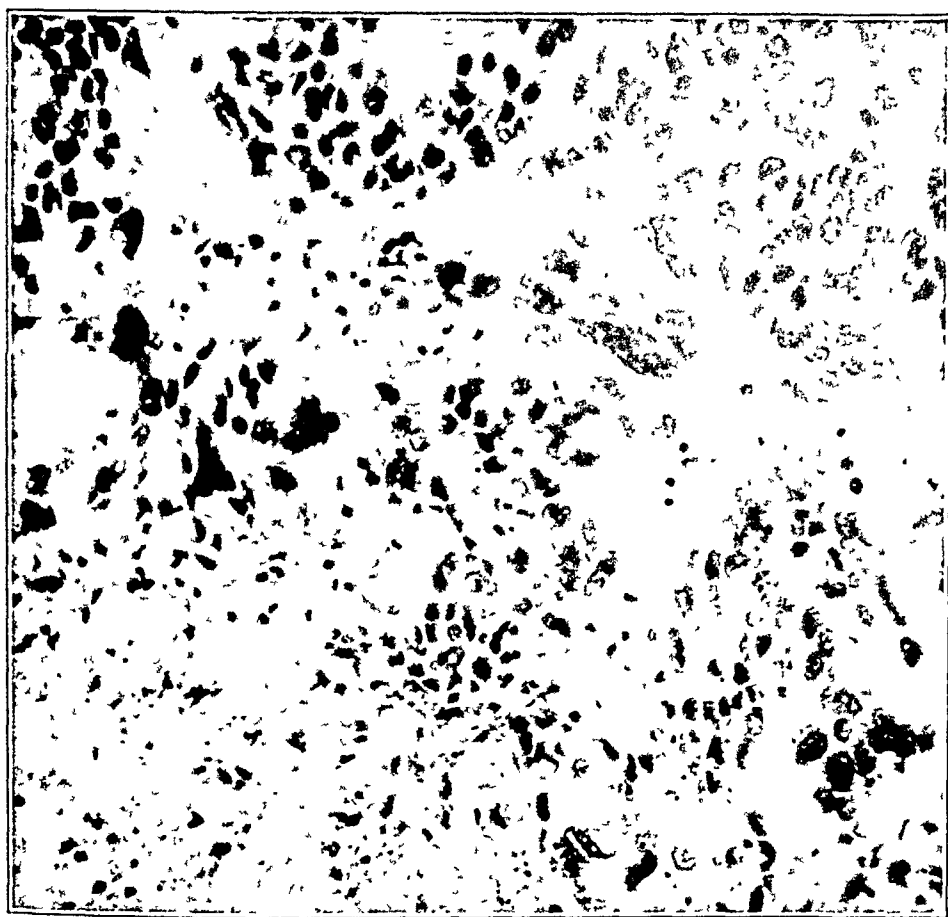


Fig. 3.—Langhans and syncytial cells in a metastatic nodule in the kidney;  $\times 175$ .

Roentgenograms of the skull showed no evidence of metastasis involving the cranial bones. The arms and thighs revealed no metastases. Roentgenograms of the chest (fig. 1) showed both pulmonary fields to be riddled with nodular shadows, sharply circumscribed and ranging in size up to 4 cm. in diameter. There was a slight pleural reaction at the base of the right lung, with a small amount of fluid. The left pleural cavity was free of fluid. The size and shape of the heart were normal.

The Mantoux test gave a negative reaction to 0.01 mg. of old tuberculin U. S. P. in forty-eight hours. Cultures of aspirated gastric contents did not yield tubercle bacilli.

There was no injection of the right globe or any proptosis or palpable masses about the eye. The right pupil was at 3 mm. and the left 2.5 mm. in diameter. Both pupils reacted to light and in accommodation. The anterior chambers had normal depth. Tension in the right eye was 10 mm. of mercury (Schiotz) and that in the left eye 13 mm.

Fundusoscopic examination of the right eye on February 19 showed that the media were clear. The disk had good color and a central cup of medium size. In the superior part of the temporal field there was a dark gray, elevated mass, which extended to the level of the macula inferiorly, to the meridian of the disk nasally and toward the superior temporal periphery; it covered an area about eight times the size of the disk. This mass was elevated about 10 D. Along the inferior border the macular fibers of Henle were seen in bold relief. In



Fig. 2.—Photograph of the fundus of the right eye taken on Feb. 25, 1947, showing the elevated mass under the retina and the hemorrhages, with light centers.

the center of the elevated area, and somewhat superiorly and temporally, were yellow-white patches and irregular hemorrhages. In the superior temporal periphery, about 7 disk diameters from the disk, there was a pigmented area about half the size of the disk, in the center of which a hole was seen in the retina. Slightly inferior and nasal to this hole was the operculum. In the inferior half of the fundus, beginning about 3 disk diameters from the disk, there was a serous detachment of the retina, which was elevated about 4 D. This detachment did not extend to the inferior temporal periphery. The left fundus appeared entirely normal.

The impression was that of metastatic tumor of the choroid of the right eye with associated retinal detachment and hole.

meridian of the optic disk and inferiorly 1 disk diameter below the level of the fovea. It also became more elevated and was seen with a +12 lens in the ophthalmoscope. New flame-shaped hemorrhages were seen on each examination. Some of these had light centers. The serous detachment in the lower part of the fundus increased in extent steadily and, when seen just prior to the patient's death, was elevated 6 D.

During the patient's course in the hospital the intraocular tension was always lower in the involved eye. The only change seen in the left eye was the pallor of the optic disk, associated with the severe anemia.



Fig. 5.—Metastatic nodule in pancreas, showing typical Langhans and syncytial cells to the left and compressed pancreas to the right;  $\times 80$ .

An attempt was made to take photographs of the fundus; but, because of the high elevation and the poor condition of the patient, the results were not satisfactory. One photograph is reproduced (fig. 2).

The general course of the illness was rapidly downhill. The patient required injections of morphine for relief of the pain in the right eye and chest. He died on February 27, ten days after admission.

*Necropsy.*—Autopsy was performed thirteen and one-half hours after death. A summary of the findings taken from the complete report made by Dr. Ralph C. Frank, of the department of pathology, follows: The pleural surfaces were studded with innumerable tumor nodules, of all sizes. Cut sections of the lung showed that all portions were involved by round, hemorrhagic and gelatinous



The quantitative Aschheim-Zondek test showed 4,000 rat units per liter of urine, a value which was very high.

On February 19 thoracentesis was performed through the ninth intercostal space on the right side, between the midscapular line and the axillary line, with removal of 850 cc. of bloody fluid. The fluid appeared like venous blood but did not clot on standing. Analysis of the fluid showed 7.6 Gm. of hemoglobin and 2,660,000 red blood cells and 8,250 white blood cells per cubic millimeter. The cultures yielded no organisms in forty-eight hours.

On February 20, biopsy of the mass in the right breast and of a lesion over the left costal margin was performed by the surgical resident, Dr. Thurer,



Fig. 4.—Metastases to the heart muscle;  $\times 80$ .

with use of local anesthesia. The report of this biopsy, by Dr. W. Jaeschke, was as follows:

"The sections showed partly necrotic and hemorrhagic tumors, composed of broad bands and irregular masses of tumor cells. Most of the cells were closely packed and moderately vacuolated and had good-sized, oval to round reticular nuclei. Mitotic figures were fairly common. Some of the cells were not clearly defined and were arranged in irregular syncytial masses of various sizes. In some cells the cytoplasm stained blue and in others pink.

"The impression was that of metastatic chorionic epithelioma."

I examined the fundus every other day. The dark, elevated mass continued to enlarge during the period of observation. It extended nasally beyond the

nodules. The hilar nodes were enlarged and involved by tumor. A small hemorrhagic nodule was observed in the posterior wall of the left ventricle and another below the aortic orifice in the endothelium. Multiple metastatic nodules were seen under the capsule of the spleen and in cross sections of the organs. Similar areas were seen in the liver. The gallbladder was not involved. The stomach had small metastases along the greater curvature. A large nodule



Fig. 8.—Metastases to the choroid of the right eye, extending to the disk;  $\times 5\frac{1}{2}$ . A serous detachment of the retina has occurred on the other side of the disk and over the tumor.

almost occluded the esophageal opening at the cardia. Three nodular areas were noted in the jejunum, but the large bowel and rectum were free from tumor. Multiple lesions were seen in the pancreas. The right adrenal gland had nodules in the medullary spaces and cortex. Both kidneys had multiple



Fig. 6.—Left testis, showing primary tumor with large areas of hemorrhage:  $\times 4$ . Compressed testicular tissue at the left side shows spermatogenesis.

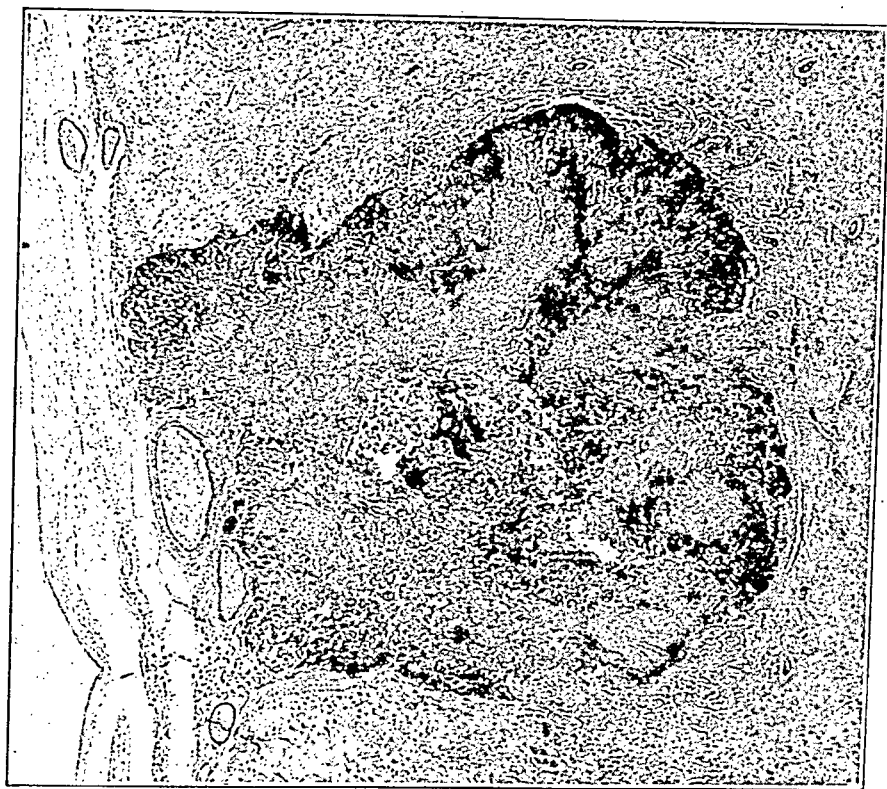


Fig. 7.—Metastatic nodule to brain just under the meninges;  $\times 23$ .

major part of the section was replaced with necrotic tumor cells and large hemorrhagic areas (fig. 6).

The right testis showed normal spermatogenesis and had no tumor. The left breast showed no metastases but was hyperplastic, with increased activity of the glandular epithelium. The pituitary glands showed no apparent pathologic process. The thyroid was normal.

The brain was studied separately by Dr. Richard Retter, of the department of pathology. Three distinct hemorrhagic nodules overlay the left occipital pole and the left parietal region. On cut section a nodule was seen in the left frontal lobe. On microscopic sections metastatic nodules were seen underlying the meninges (fig. 7). There was localized thickening of the meninges over the nodules. Surrounding the nodules were shrinking and pyknosis of the neurons and moderate increase in glial elements.

I removed the right eyeball at the time of autopsy, or about fourteen hours after death, and fixed it in Zenker's solution. The report from the laboratory of ophthalmic pathology was made by Dr. Peter Duehr. Grossly, the tumor measured 5 by 10 mm. The retina was detached over the tumor mass (fig. 8).

Microscopic examination (fig. 9) revealed that the eye was of average size. The interior of the eye contained a tumor occupying about one sixth of the globe. The tumor was located in the choroid, extending from the optic nerve forward to pass the equator. The main mass of the tumor was filled with blood, making study of the cells impossible. Around the periphery of the tumor the cells were well defined. The tumor cells contained large, various-sized, round to oval nuclei, which stained pink and were reticulated. The nuclei were closely packed, and the cytoplasm was sparse. Among the closely packed cells were vascular spaces, which contained only a few blood cells and much foamlike and granular, pink-staining material. Mitotic figures were common. The retina was edematous and detached. The cornea was devoid of epithelium. The anterior chamber was open. The iris and ciliary body were not remarkable. The sclera and optic nerve appeared normal.

The final diagnosis was primary chorionic epithelioma of the left testis, with metastases to the spermatic cord, kidneys, right adrenal body, liver, pancreas, spleen, jejunum, stomach, heart, lungs, brain, subcutis, right choroid and right breast. There was also gynecomastia and fibrocaseous tuberculosis of the liver and spleen.

#### COMMENT

The case presented is, as far as we can determine, the fourth case of chorionic epithelioma with metastasis to the choroid observed in a man. The initial complaint, which brought the patient to the ophthalmologist, was failure of vision in the right eye. He had had a persistent cough, suggesting metastases to the lungs, two months previously. After the visual disturbance, the course was rapidly downhill, the patient dying within three weeks.

The origin of the tumor was in the left testis. Metastases were observed in the cerebral cortex, the choroid of the right eye, both lungs, the heart, stomach, small intestine, kidneys, liver, spleen, pancreas, the right adrenal gland, the right breast and the subcutaneous tissue. No metastases were noted in the roentgenograms of the bones. None was found in the pituitary body. The urine showed a high concentration

nodules under the capsule, being more numerous in the right kidney. The ureters contained no metastases. The prostate gland and seminal vesicles appeared normal. The right testis was normal, but the left was completely replaced with hemorrhagic tumor tissue. There was an area of tumor tissue just above the left testis in the spermatic cord. The thyroid was normal.

*Microscopic Examination.*—The tumor tissue had an extremely malignant appearance, with great variations in the size, shape and chromaticity of the nuclei. Mitotic figures were frequently seen. The typical cells had round or

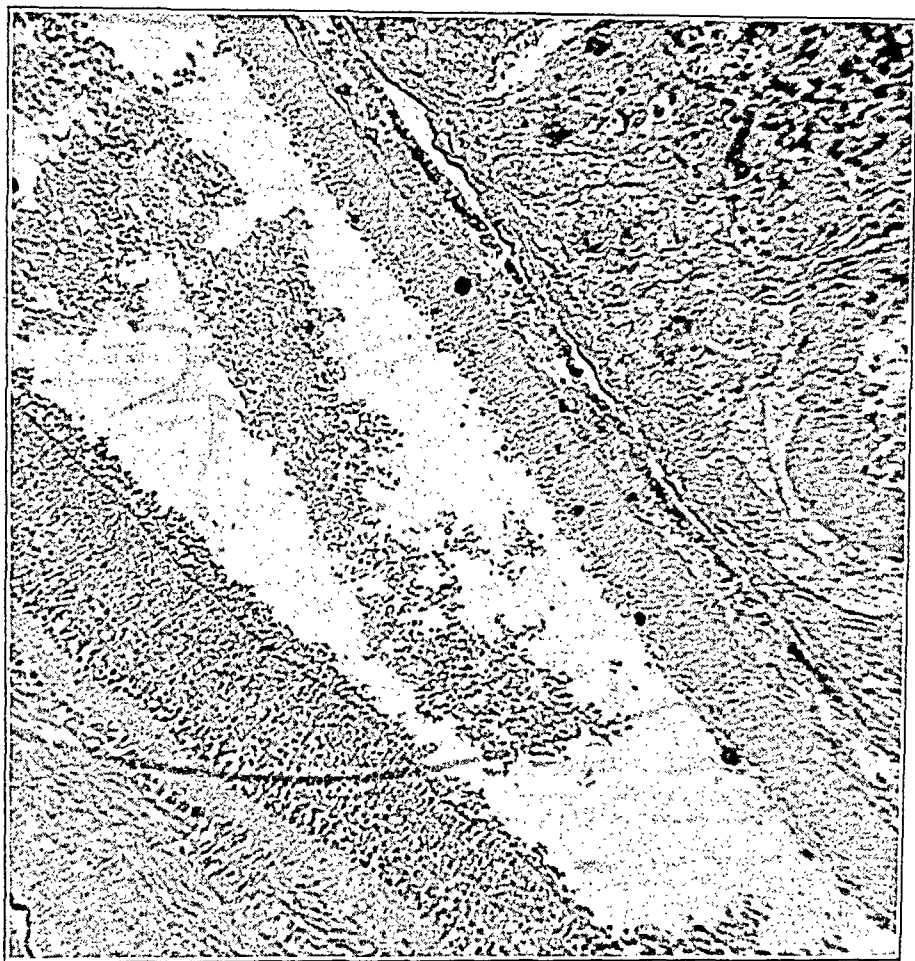


Fig. 9.—Metastasis to the choroid of the right eye (right side);  $\times 90$ . Serous detachment of the retina has occurred over this nodule; the separation is within the layer of rods and cones.

ovoid nucleoli (fig. 3). Other types had darker nuclei. The cytoplasm was basophilic, but for the most part was poorly demarcated, and frequently syncytia of cells were seen in which only the nuclei were distinct and the cell borders were completely lost. Necrosis and hemorrhages were of frequent occurrence in the various sections. The nodules containing the typical cells were seen in the heart (fig. 4), lungs, spleen, liver, pancreas (fig. 5), submucosa of the stomach and jejunum, cortex and medulla of the right adrenal gland and both kidneys. The left testis showed spermatogenesis in the remaining testicular tissue, but the

# VOLUNTARY DISSOCIATION OF THE ACCOMMODATION AND THE CONVERGENCE FACULTY

Two Observations

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MANY persons have volitional control of convergence; at the command, "Cross your eyes," they are able to do so with ease. Others cannot, but after a period of tutelage they acquire the faculty. A simple exercise to bring this about consists in having the subject regard a pencil at the punctum optimum and then hold his eyes in their assumed position by "imagining" the pencil after its withdrawal, demonstrating an obviously conscious influence. This control probably can be conditioned to occupy a subconscious level, since the position can be held in the face of distracting influences and the diversion of conscious thought. A patient described by Walsh<sup>1</sup> had apparently developed great skill in the voluntary control of her convergence and in voluntary alternate suppression. A third group of persons is made up of those who seem quite unable to acquire volitional control of convergence. It has been demonstrated that these voluntarily induced convergences are usually accompanied with corresponding increases in the accommodation and by miosis; conversely, it is easily possible, with numerous devices, to disassociate the accommodation and the convergence. Those who experiment with ocular gymnastics often find that they can accomplish this disassociation voluntarily under certain conditions. Years ago I acquired the not uncommon ability of getting vivid stereoscopic effects with Brewster type pictures without the use of the Brewster instrument. A friend employed in aerial map making introduced me to this phenomenon. He used aerial photographs taken over rugged but familiar terrain for the demonstration. His employment duties required him to insert these slightly dissimilar pictures into a modified stereoscopic device and from the resultant three dimensional effect to create the required maps, including to some extent the regional topography. He had discovered that he could get the same effect impressed on his visual cortex without the use of the instrument, and he acquired such facility in the technic that much of his work was thereafter done unaided. The phenomenon was

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1. Walsh, F. B.: *Clinical Neuro-Ophthalmology*, Baltimore, Williams & Wilkins Company, 1947, p. 275.

of estrogens. Photographs of the fundus were taken, but the results were not satisfactory because of the high elevation of the retina and tumor. One photograph is reproduced (fig. 2). The intraocular tension was lower in the eye involved. In previous reports the tension was elevated, and the eyes had to be enucleated because of glaucoma. The typical Langhans and syncytial cells were seen both in the primary tumor and in the metastases.

Of the 4 cases of testicular chorionic epithelioma with metastasis to the choroid, the right eye was involved in 3. Reichling,<sup>5</sup> in his incomplete report, did not specify which eye. The primary source was from the right testis in 2 cases and from the left testis in 2 cases. The patient lived two months after onset of visual disturbance in Reichling's case, one month in MacDonald's, three weeks in mine and two weeks in Godtfredsen's.

#### SUMMARY

A case of a testicular chorionic epithelioma with metastases to the choroid of the right eye is presented. Only 3 other cases of occurrence in men have been reported. Three cases with metastases to the choroid in women from chorionic epithelioma of the uterus have been reported.

In the present case, metastases were observed in the brain, breast, stomach, intestine, liver, adrenal gland, subcutis, heart, lungs and pancreas.

312 East First Street.

and appears slightly magnified. If the hexagonal mesh were moved physically to a point 1 foot beyond the window frame, the mesh would appear smaller, in keeping with the law of the square of the distance; moving it psychically to this position makes it larger by an apparent 20 per cent (estimated). It is then easy to increase the accommodation slightly to clarify the burglar mesh in its illusory position, then to increase both accommodation and convergence to see the burglar mesh in its true position and, finally, to increase both accommodation and convergence still more to see the hexagonal mesh in its true position; here it appears to be about 20 per cent minified from its apparent size in the illusory position.

The ocular gymnastics per se are of little interest, and the illusion is easily explained. The hexagonal mesh is of such size that the eyes are focused on adjacent meshes in the illusory position; the gas bubble patterns serve as effective orientation marks. The cerebral picture integrated from these two almost identical meshes shows a composite, or summation, of the bubble patterns of the two meshes, or true fusion. This means that the lines of fixation of the two eyes cut corresponding points of adjacent meshes 2 feet away and intersect each other 3 feet away. The eyes, being converged to the 3 foot plane, are under about 1 meter angle of convergence. By an increase in disassociated accommodation to 1.5 D., the illusory image is clarified but does not leave its illusory plane. It seems reasonable, therefore, to assume that psychic localization of the horopter in space is predicated on the convergence faculty primarily and on the accommodative faculty secondarily or not at all.

In studies on stereoscopic accuracy in relation to the duration of the illumination, Langlands<sup>2</sup> found that a spark discharge of  $\frac{1}{150,000}$  second's duration permitted considerable accuracy in stereoscopic localization. As the exposure time increased, the stereoscopic accuracy also increased; this increase was most rapid in tests with time intervals between 0.1 and 0.5 second. This zone of rapid increase corresponds with the action time of the ocular muscles, but Duke-Elder<sup>3</sup> expressed doubt that differentiations so fine are based on proprioceptive muscular impressions. While stereopsis is the summational effect of numerous contributory factors, I believe that psychic localization of the horopter is predominantly an expression of convergence, and I find it difficult to deny a place to proprioception. The deterioration of stereopsis at great distances is in keeping with the infinitesimal variations in convergence involved. The spark discharge studies of instantaneous stereopsis seem compatible with this view, as the brain is merely comparing the flash with the horopter; it is not necessary for one to shift the horopter to appreciate whether a spark lies without or within it or to estimate the distance quantitatively. The time factor thus becomes of secondary importance. It is necessary only for the spark to record itself on disparate points of the immobile retinas in order

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2. Langlands, T.: *J. Optic. Soc. America* 28:45 and 83, 1927; cited by Duke-Elder.<sup>3</sup>

3. Duke-Elder, W. S.: *Textbook of Ophthalmology*, St. Louis, C. V. Mosby Company, 1944, vol. 1, p. 1078.



readily identifiable as a voluntary disassociation of the accommodation and the convergence faculty, and I was able to duplicate his control promptly, with a vivid sensation of peaks and canyons resulting from the integration of his photographs. One smaller pinnacle which I had scaled a number of times afoot seemed fairly to shoot up at me from the familiar creek bed below. Since that time, unaided stereoscopy has continued to be easy with suitable material. This phenomenon is, of course, common among ophthalmologists and among roentgenologists; many of the latter learn to get a stereoscopic effect from their films unaided merely by selecting a favorable distance from their view boxes. I recount this as information preliminary to the following observation.

The observation resulted from my idly looking out a window. This window beside my desk is 24 inches (60 cm.) from my eyes as I gaze over the rooftops at an attractive distant building. The glass in this window is reenforced by embedded wire mesh, the meshes being regularly hexagonal and about 1 inch (2.5 cm.) in diameter. About 4 inches (10 cm.) beyond the reenforced glass is a stout burglar screen of another type of wire mesh, the meshes in this case being square, regular and slightly more than  $\frac{1}{2}$  inch (1.3 cm.) in diameter. The burglar screen was put in place because of a fire escape outside the window; the fire escape is 2 feet (60 cm.) in width and is guarded by an outer rail of slender steel bars. While gazing at the distant building (about 1 mile [1.6 kilometers] away) I became aware that the hexagonal pattern of the glass-reinforcing wire was covering my view in a curious manner. It conveyed the impression of lying about 12 inches (30 cm.) beyond the window frame; that is, it appeared as a mesh wire fence dividing the fire escape into two lanes. I fixed the impression strongly in my mind and then cautiously increased my accommodation from infinity to the illusory position of the wire pattern about 3 feet (90 cm.) away. By doing this slowly, I found myself able to bring the details of the hexagonal meshwork into sharp, optimum focus, seeing all visible details of the complex little patterns of gas bubbles embedded in the glass around the wire. I was able to scrutinize this pattern as acutely and subconsciously as though it were a sheet of newspaper 3 feet away. At this time the burglar screen (square) mesh appeared slightly blurred but seemed about 3 inches (6.3 cm.) nearer my eye than the hexagonal mesh, thus appearing to be displaced outward from its true position perhaps 9 inches (22.5 cm.). During this illusion the slightest motion of the head created multiple plane parallax shifts of these various grills, in keeping with their true positions; the parallax was therefore antagonistic to the illusory impressions, and yet the antagonism was not strong enough to disrupt the illusion.

I have repeated the optical illusion many times and find it no longer necessary to begin the experiment by focusing on the remote building (infinity). I can focus on the hexagonal mesh within the window glass (at 24 inches, or with about 1.5 D. of accommodation and 1.5 meter angles of convergence), and then, by relaxing a trifle, cause the optical illusion mesh to appear halfway across the fire escape (at 36 inches [90 cm.], or with about 1 D. of accommodation and 1 meter angle of convergence). This mesh appears somewhat blurred if all function is arrested at this point; but if the accommodation is again carefully increased to 1.5 D. and the convergence is left at 1 meter angle, the blur disappears and the wire with its little bubbles takes on normal clarity, retains its illusory position

eye pieces and experiences obvious separation of the images. By selecting a small defect or a preplaced ink dot on one of the slides (preferably for the dominant eye), the subject may suppress the other eye and accommodate to maximum acuity on the defect, and then on the whole slide. This image may be made crisp and clear, and held that way. Then, by volitional convergence control (actually, a reduction of convergence) the diplopia can be made to lessen. When the two images finally come very close to each other, they will abruptly slip together with a sudden motion and a simultaneous magnification in size. The magnification must be of central (not lenticular) origin, since the monocular slide having the defect has been kept in sharp focus throughout. If the diplopia disappears at the same instant that the monocular slide defect is gotten into correct focus, the demonstration is incorrect, and the tube divergence must be increased slightly to increase the diplopia. A position can be found which will give a clearly obvious time lag between the correction of the accommodation and the correction of the diplopia, with the described abrupt change in size. The only change occurring at the instant of sudden magnification is a simultaneous sudden decrease in convergence.

My second, and more interesting, observation in this matter is related to a curious case which came to my attention; I regret that she can no longer be reached for better systematic study. The woman, in her early thirties, presented herself for refraction, with no complaints except the slight inadequacy of her glasses. Her refractive error was of no consequence, and a minor change restored satisfactory acuity. During the refraction an apparent right hyperphoria of  $2 \Delta$  for distance was found, but for some reason no duction tests were performed at this visit. She was given instead a pair of temporary prism clip-ons to wear over her old glasses. She wore the prisms for two weeks and returned to report complete indifference to them; they had no effect whatever, either favorable or adverse. At this time the duction measurements were taken and a remarkable picture appeared. The ductions seemed almost unlimited in all directions. She would promptly overcome a 5 D. prism base down before either eye, describing diplopia only during the fraction of a second it required for her to overcome the prism. A 5 D. prism base up was accepted just as readily. Vertically placed prisms of 5 D. with bases opposite before the two eyes did not disturb her; she again described only a fleeting instant of diplopia. Ten diopters per eye (a total of 20 D.) if applied gradually was overcome.

She was intelligent and cooperative and presented herself for periodic examination a number of times, displaying a ready grasp of all questions and much insight. She had always considered her eyes normal and denied there being any personal or familial history of strabismus. The existence of her ocular novelty did not weigh on her in the least, and she returned only to enable me to observe this unusual performance further. Under slowly moving Risley rotary prisms I repeatedly watched the behavior of her eyes. The eyes would deviate independently toward the apexes of the prisms to a remarkable degree. By increasing the base-down prism before one eye, I could make the eye turn higher and higher at the same time that base-up prism was forcing the other eye down.

to establish its position in relation to that of the horopter. The position of the horopter, while constantly varying, is at any instant available for instantaneous comparisons.

In his discussion of lesions involving the posterior oculogyric mechanism, Walsh <sup>4</sup> mentioned the case reported by Holmes and Horrax, in which the patient, after a military head injury, sustained no paresis of the extraocular muscles but was unable to converge on a near object and lost his stereopsis. Walsh <sup>5</sup> quoted Adler in listing the mechanisms involved in perception of depth:

(7) Accommodation: As each eye must be accommodated for objects nearer than infinity in order to see them clearly the amount of accommodation necessary may be of some aid in determining their position. This is a relatively unimportant factor in man, however.

This small part played by pure accommodation must be very minor. It is extraordinarily difficult to estimate the distance of a soap bubble above one against a cloudless sky with one of the eyes covered. The integration of two images for binocular depth perception introduces, among other things, the convergence factor and the dissimilarity of the images. These also can be readily separated by many means. I recently saw some three dimensional material prepared from photographs in such a manner that the topographic, or relief, effect was intentionally exaggerated through the stereoscope; the binocular resultant was startling in its stereoscopic impact, but the mean level of the picture was stable; it lay on the horopter determined by the state of the eyes and the viewing mechanism. The horopters for the various levels of the picture involved changes in convergence, but no changes in accommodation.

The increase in the disassociated accommodation during my illusion with the grills accounts for the magnification of the illusory image; but since the eye is accommodated 1.5 D. to see the true image in its true position and also 1.5 D. to see the illusory image clearly, this increase is not a real one; it is only relative to the convergence. Thus, the convergence also becomes the only variable in action to affect the image size as well. It is possible to demonstrate this on the major amblyoscope easily. Throughout the experiment the tubes are left locked after a selected position has been found. One may place a moderate burden on the accommodation, if desired, by putting —3 D. spheres in the cells of the eyepieces. Then, by trial and error, a position of relative divergence is located for the tubes in which horizontal diplopia exists but which can be overcome in a few seconds. The tubes are locked. The subject returns his eyes to the

4. Walsh,<sup>1</sup> p. 299.

5. Walsh,<sup>1</sup> p. 253.

information of possible value. I believe that she maintained her almost perfect, and remarkably deceptive, cosmetic and functional binocularity by means of exceedingly rapid alternation—alternation in the psychic or integrative sense—and that visible (slowed down?) physical alternation occurred only under induced stress with the impediment of fatigue.

Her interesting exhibition may have the significance of a “missing link” in the fusion problem. As a rather crude demonstration of this mechanism, one may mentally picture two glass tubes 1 meter in length and a few centimeters in diameter standing erect, side by side. One may then picture a large cork in each tube, the cork being slightly smaller than the tube, so that it can drop through with perfect freedom and no friction and yet fit the tube reasonably well. One may then imagine a mechanical device in the bottom of each tube which will project or shoot small round metal shot upward against the bottom of each cork. By synchronization of the frequency and velocity of the upward streams of shot, it would be a simple matter to make the corks rise equally in the tubes. Firing the shot with greater force would send the corks higher; reducing the force of the shot would let the corks ride lower in their cylinders. If the shots were fired with sufficient frequency, the inertia of the corks would cause them to ride motionless in their tubes; reducing the number of shots per second below the inertia reaction time of the corks would impart a visible jiggling or flutter to the corks. This simple experiment is admittedly crude, with various mechanical flaws, but may serve to demonstrate the idea. I have therefore toyed with the hazardous thought that this patient may hold a clue to the nature of fusion; that fusion may indeed be based on a rapid neurologic alternation of two dissimilar images, with ocular parallelism enforced in most people by the speed of the alternation. This patient’s lack of true stereopsis does not necessarily militate against this view if her condition is considered a borderline one, lying between the physiology of “normal” binocularity and that of manifest strabismus. As a corollary, one might again revive the theory that strabismus occurs in persons who have defective synchronization of the paired oculoneural “stroboscopes.”

#### SUMMARY

Two observations on the voluntary dissociation of the accommodation and convergence faculties are discussed. The first observation suggests that the psychic concept of the location of the horopter in space is primarily related to convergence, rather than to accommodation. It also suggests that the psychic magnification of near objects and minification of distant objects in excess of that based on the law of the square

ward. The eyes could be readily observed over the edges of the Risley prisms, and the effect was disconcerting. The cover test performed repeatedly by several trained observers failed to reveal any abnormality under closest scrutiny except the trace of right hyperphoria. She gave every evidence of cosmetic and functional binocularity to several observers on routine examination. Under the higher prism stresses she would describe distortions of various types; for example, a square window would be converted to an oblique lozenge, but would never appear double. I was unable, in my perplexity, to record trustworthy figures for her ductions; she seemed to reach variable, but always extreme, end points in accordance with anatomic limitations and fatigue. The more vigorous applications of prism would cause fleeting dizziness, which she calmly ascribed to distortion of her field. She rejected the higher strengths of vertical prism clip-ons for interval wear between visits because of the distortion, but never because of diplopia. She accepted up to 6 D. with base up or base down on either eye for prolonged wear (days) with the intelligent description of only minor nuisance value. On removing the clip-ons, one could see the eyes in their abnormal positions for an instant before they assumed a common level; she described diplopia during these quick adjustments.

The horizontal ductions behaved similarly, both with Risley prisms and with the major amblyoscope. As base-out effect was increased, she described the usual minification and recession of her image, but would hold a single image to the maximum available with the instruments. The eyes would visibly be turned in very strongly and would elicit a description of a slight and transitory pulling sensation in the areas of the outer canthi; I presumed that these sensations originated from the check ligaments. A base-in effect caused the eyes to diverge; beyond 20  $\Delta$ , she seemed to lose control in some manner which she could never fully explain but which she firmly insisted was not doubling of her images. As the base-in effect was increased, she described magnification of her image, which seemed to draw closer. I believe her confusion at 20  $\Delta$  base in was probably due to this magnification and approximation, with loss of the image within her near point; i. e., it was due to inability to diverge beyond 20  $\Delta$  and accommodate for near point simultaneously! On the Keystone stereoscope, with the familiar stereopsis card, she was unable to demonstrate any third degree fusion on repeated trials. She readily demonstrated pseudostereopsis with coins, pencils, and the like, but her monocular behavior was as good as the binocular. A Verhoeff stereoptor® unfortunately, was not available.

In an effort to determine a basis for possible prism needs, I asked her to return some evening when she felt unusually fatigued; she did so and provided another most interesting exhibition. On the major amblyoscope, I first applied divergence; when she reached the area of 12  $\Delta$ , I thought I detected a tremor or flutter in her eyes. Repeating the maneuver several times very slowly and watching each lateral limbus with a hand loupe, I found a variable point in the 12  $\Delta$  divergence area where she would display a very fine conjugate horizontal oscillation, too rapid to count, but probably of almost the flicker or frame frequency of early motion pictures. At this threshold she still denied diplopia but described a rather pronounced blurring of her image. Beyond this point she elected left fixation and described immediate diplopia as the right eye resumed cosmetic parallelism.

I have deeply regretted the haphazard nature of those examinations, for subsequent deliberation convinces me that this woman's ocular behavior holds

## A SURGICAL APPROACH TO THE INFERIOR OBLIQUE MUSCLE

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DR. JAMES WATSON WHITE was the first to operate on the inferior oblique muscle at its insertion, when, in 1936, he performed a recession of its tendon on the globe. He described the surgical technic, and the highly successful results obtained, in the June 1943 issue of the *American Journal of Ophthalmology*.<sup>1</sup> The procedure was immediately recognized as a most significant contribution to ophthalmic surgery, and repetition by others of Dr. White's faultless result attests its value.<sup>2</sup> It seems appropriate, therefore, to refer to this operation—the recession of the tendon of the inferior oblique muscle—as the James Watson White operation.

In doing the White operation at the New York Eye and Ear Infirmary, without detaching the lateral rectus muscle, I have not found the usual approach through the conjunctiva completely satisfactory. The incision is usually made downward from the tendon of the lateral rectus muscle, and at no place does it directly expose the inferior oblique muscle. A search of the literature did not reveal any suggestion for a better exposure. An approach which seems an improvement is therefore submitted. This method was developed in the clinic of Dr. Raymond Emory Meek.

Surgical approach to the inferior oblique muscle at its insertion, when the lateral rectus muscle is not detached, is not an easy task.<sup>3</sup> With the method I have seen used, the surgeon locates the muscle by making blind sweeps with a muscle hook. If and when the muscle is brought into the conjunctival wound, it is hidden by the bulbar fascia of Tenon. This fascia must be dissected to expose the muscle and its tendon. Each time the muscle slips off the hook, this procedure is repeated, resulting in mutilation of the bulbar fascia of Tenon. Good exposure and convenient working conditions are only occasionally

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†Dr. Johnson died July 13, 1948.

Read before the New York Academy of Medicine, Section of Ophthalmology, Jan. 20, 1947.

1. White, J. W.: Surgery of the Inferior Oblique At or Near the Insertion, *Am. J. Ophth.* 26:586 (June) 1943.

2. McDannald, C. E.: Unpublished data.

3. Berens, C., in discussion on White.

of the distance is predicated on convergence primarily, rather than on accommodation.

The second observation involves an unusual case of fusion anomaly in which lifelong functional parallelism appeared to depend on alternation at or above the frequency of flicker. It is believed that this case may be evidence in favor of the theory of physiologic alternation as a basis of fusion.

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obtained. As other troublesome accidents, the surgeon may (1) seize the inferior rectus muscle on the muscle hook by mistake, either alone or with the inferior oblique muscle; (2) sever the inferior rectus muscle from the globe, because he has mistaken it for the inferior oblique muscle; (3) injure the inferior rectus muscle necessitating later resection; (4) split the lateral rectus muscle by catching its lower half on the muscle hook, and (5) sever or damage the branch of the oculomotor nerve supplying the inferior oblique muscle.

These problems are all encountered as a consequence of the remoteness of the usual conjunctival incision from the muscle. When the incision does not overlie the inferior oblique muscle, direct exposure is impossible. Placement of the new incision and the technic of exposure to be described afford a direct view of at least a portion of the muscle, and the surgeon is thus enabled to pass the muscle hook more correctly and with greater ease.

#### OPERATIVE TECHNIC

The globe is held in the position of extreme adduction by traction exerted on a suture placed in the limbus on the lateral side of the cornea and held by an assistant. The suture used is 00 braided silk on an atraumatic needle. If the limbal suture is not used, adduction may be obtained by means of a muscle hook placed under the tendon of the lateral rectus muscle.

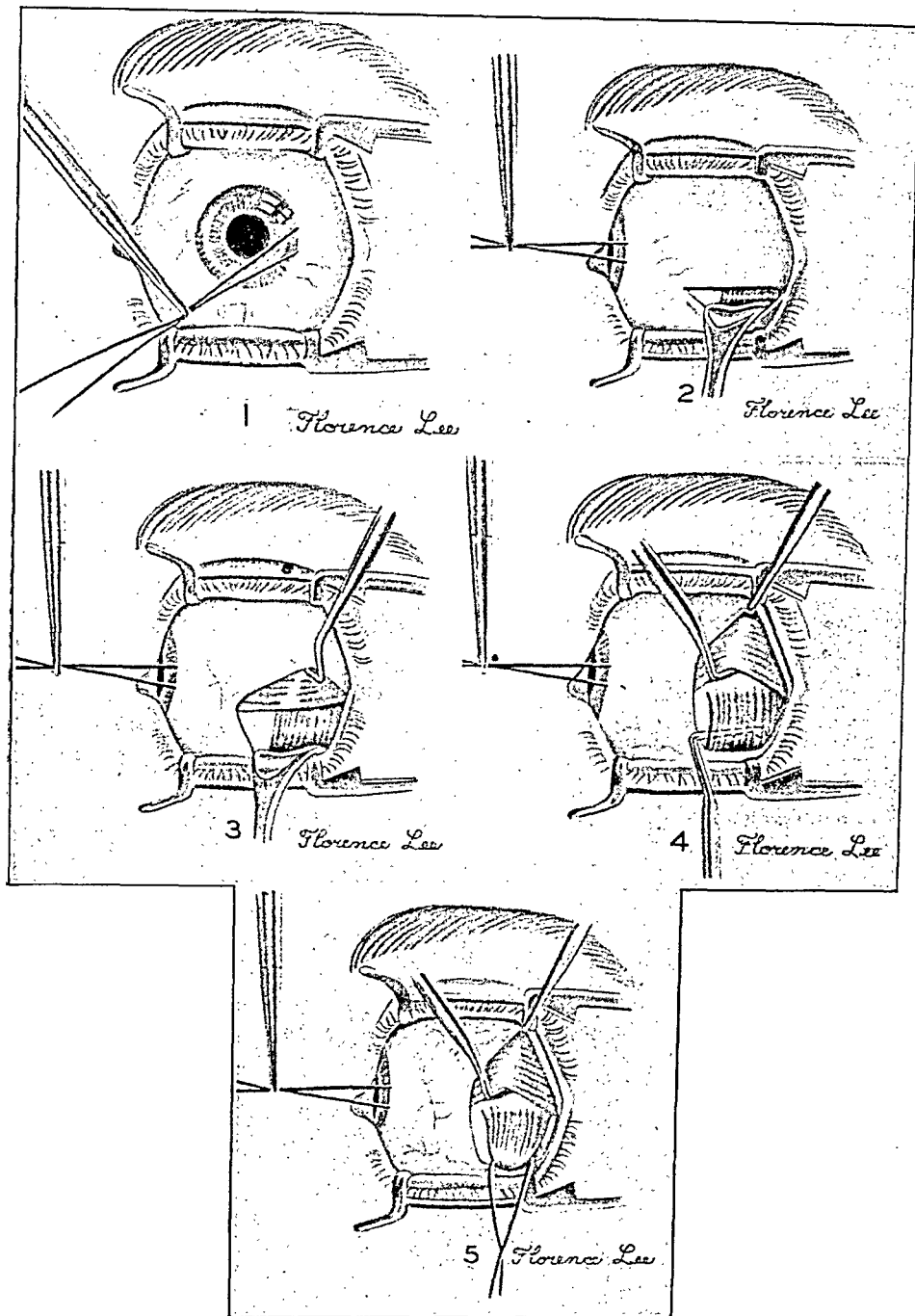
With a Lester forceps the conjunctiva is picked up just below the lower border of the lateral rectus muscle, at a point midway between the limbus and the outer canthus. The conjunctival incision is continued horizontally along the lower border of the lateral rectus muscle to the lateral fornix.

The bulbar fascia of Tenon will then be exposed in the conjunctival wound. At the outer canthus this fascia is cut and spread apart with a pair of Stevens scissors. The inferior oblique muscle will be seen through the opening in Tenon's fascia. The fascia is retracted with a Desmarres retractor. The extent of muscle thus exposed varies from its anterior border alone to over one-half its width. The amount of muscle exposed is directly proportional to the width of the palpebral fissure, the amount of backward bowing of the lateral orbital margin, the length of the lateral check ligaments and the length of the optic nerve. It varies inversely with the amount of the retrobulbar injection. The amount of muscle exposed also varies with the position of insertion of the muscle into the sclera—the closer to the cornea the insertion, the greater will be the exposure of the muscle.

A hook is next passed around the muscle. If any fascia is included, another hook should be placed so as to exclude Tenon's fascia from its grasp. A suture (from 0 to 000 in size) is next passed around the muscle. The ends of the suture are secured by a suture clip. Should the muscle slip off the hook, the suture enables the surgeon to replace the hook without further trauma to Tenon's fascia. Should the hook not be replaced, a recession operation may be completed without it.

With Lester forceps and a Stevens scissors, Tenon's fascia is dissected away from the muscle and its tendon. Under no condition should any dissection be made along the muscle more than 5 mm. beyond its insertion because of the danger





(1) A traction suture is placed in the temporal limbus. (2) The globe is held in the position of extreme adduction by traction on the suture; the drawing shows the position of the conjunctival incision and its relation to the inferior oblique muscle, which is exposed to view by the Desmarres retractor. (3) A muscle hook elevates the upper edge of the opening in the conjunctiva and Tenon's fascia in order to show the lateral rectus muscle overlying the global end of the inferior oblique muscle. (4) A muscle hook elevates the conjunctiva, with exposure of the lateral rectus muscle, which, in turn, is elevated by another hook, with exposure of the insertion of the inferior oblique muscle. (5) A suture replaces the muscle hook around the inferior oblique muscle.

During the actual surgical procedure, neither the upper edge of the conjunctival incision nor the lateral rectus muscle need be retracted.

# STUDIES OF THE EYE WITH RADIOSODIUM AUTOGRAPHS

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**A**RTIFICIAL radioactive isotopes were introduced for turn-over studies on the eye by Kinsey, Grant, Cogan, Livingood and Curtis.<sup>1</sup> These investigators used Na<sup>24</sup>, P<sup>32</sup> and Cl<sup>38</sup> in their work with rabbits. Recently, Wang<sup>2</sup> studied the movement of radioactive sodium and chloride in dogs, whereas Visscher and Carr<sup>3</sup> (in dogs) and Scholz, Wilde and Cowie<sup>4</sup> (in guinea pigs) limited their study to radiosodium. These investigations revealed the steady state ratios of the tracer elements between plasma and ocular fluids and the turnover rates of these constituents in the aqueous humor. The investigations of Visscher and Carr<sup>3</sup> and Wang<sup>2</sup> included studies on the rate of entrance of the radioactive elements into the cerebrospinal fluid. All these results confirmed the impression of the usefulness of radioactive elements as tracers in biologic studies. Quantitative data of great accuracy were secured by measuring (with the Geiger-Müller counter) radiations

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Supported by the Knapp Memorial Foundation.

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Read in part at the Three Hundred and Eighty-First Meeting of the New England Ophthalmological Society, Boston, Feb. 18, 1948.

1. Kinsey, V. E.; Grant, W. M.; Cogan, D. C.; Livingood, J. J., and Curtis, B. R.: Sodium, Chloride and Phosphorus Movement and the Eye Determined by Radioactive Isotopes, *Arch. Ophth.* **27**:1126-1131 (June) 1942.

2. Wang, J. C.: Penetration of Radioactive Sodium and Chloride into Cerebrospinal Fluid and Aqueous Humor, *J. Gen. Physiol.* **31**:259-268 (Jan.) 1948.

3. Visscher, M. B., and Carr, C.: The Rate of Entrance of Radio Sodium into the Aqueous Humor and Cerebrospinal Fluid, *Am. J. Physiol.* **142**:27-31 (Aug.) 1944.

4. Scholz, R. O.; Cowie, D. B., and Wilde, W. S.: Studies on the Physiology of the Eye Using Tracer Substances: I. The Steady-State Ratio of Sodium Between the Plasma and Aqueous Humor in the Guinea Pig, *Am. J. Ophth.* **30**:1513-1515 (Dec.) 1947. Wilde, W. S.; Scholz, R. O., and Cowie, D. B.: Studies on the Physiology of the Eye Using Tracer Substances: II. The Turnover Rate of Sodium in the Aqueous Humor of the Guinea Pig: Methods of Analysis, *ibid.* **30**:1516-1523 (Dec.) 1947.

of injury to the nerve. This nerve enters the posterior border <sup>4</sup> or the upper border <sup>5</sup> of the muscle about 12 mm. from the globe. The inferior oblique muscle is now ready for operation.

#### COMMENT

The usual approach for exposure of the inferior oblique muscle has been discarded, for the reasons stated. With the method described, an incision is made parallel with the external rectus muscle and extended along its lower border to the lateral fornix; thus the inferior oblique muscle is more satisfactorily exposed and is more readily accessible.

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4. Whitnall, S. E.: *The Anatomy of the Human Orbit and Accessory Organs of Vision*, ed. 2, London, Oxford University Press, 1932, p. 279.

5. Wolff, E.: *The Anatomy of the Eye and Orbit*, ed. 2, Philadelphia, The Blakiston Company, 1940, p. 182.

graphic plate, and by Evans,<sup>9</sup> in mounting the tissue section directly on the photographic emulsion of a plate or film. In these processes, the preparation was first developed photographically and then subjected to histologic staining procedures. The reduced silver grains of the emulsion were closely superimposed on histologic details and were well alined to the finer structures of the thin sections.

In the present study, a first attempt was made to use radiosodium for radioautographic studies of the tracer in the eye. In view of the relatively short half-life of this radioisotope and the fact that there is no preferential binding of sodium to structural and chemical constituents of the ocular tissues, the technic in the work with iodine and other isotopes had to be modified or replaced with new methods.

#### MATERIALS AND METHODS

Two principal methods of radioautography were selected. First, the technic developed by Evans<sup>9a</sup> for studies on the distribution of iodine in the thyroid gland was applied to thin tissue sections of eyes of experimental animals. Since a description of this procedure is not readily available to ophthalmologists, it will be presented here in brief form as it was used on the eye.

The tissue was fixed and dehydrated in acetone or absolute alcohol (three changes, three to five minutes in each change), embedded in paraffin and cut in sections 10 to 12 microns in thickness. Ribbons containing two or more sections each were spread on water at approximately 42 C. and then quickly transferred to a vessel with cool water. In the darkroom, films (kodak dental x-ray film ultraspeed®) or plates (kodak lantern slide medium contrast plate® 2 by 2 inches in size) were slipped under the floating sections to lift them from the water. The preparations, consisting of the sections on films or plates, were dried by a fan and stored in light-tight boxes. On the following day, the paraffin was removed in a xylene bath, and (after drying) the preparations were returned to the storage boxes for the desired time of exposure. The photographic films or plates with the tissue sections in place were developed in a developing solution (Eastman D-11,® for example) for two to five minutes and further processed in the usual way. The sections were then stained with Delafield's hematoxylin (overstained) and passed through acid water; the emulsion on the back of the film was removed by scraping, and the sections were then passed through ammonia water, stained with eosin, dehydrated, cleared and mounted in balsam. The tissue for the microscopic sections was obtained in three ways: (1) by removing the iris and ciliary body after opening the globe by an equatorial section; (2) by keeping intact the entire anterior segment without lens; (3) by cutting slices from frozen globes adjacent to the vertical meridian plane.

The second method used was one of gross examination and has not been described before. The experimental animal received the radioactive tracer material by local or systemic route and was killed after a planned interval by intravenous

9. Evans, T. C.: (a) Preparation of Radioautographs of Thyroid Tumors for Study at High Magnification, *Radiology* **49**:206-213 (Aug.) 1947; (b) Radioautographs in Which the Tissue Is Mounted Directly on the Photographic Plate, *Proc. Soc. Exper. Biol. & Med.* **64**:313-315 (March) 1947; (c) Selection of Radioautographic Technic for Problems in Biology, *Nucleonics* **2**:52-58 (March) 1948.

emitted by the radioactive elements in samples of ocular fluid after their introduction under various conditions.

Although the counter technic eliminates many errors and facilitates quantitative studies, it does not provide maximum information on the topographic relation of the tracer atoms within individual structures of the eye. Such a purpose seems better served by radioautography, which under certain conditions is suited to determination of actual location and differences of concentration of the radioactive elements with respect to histologic landmarks. The technic makes use of the photographic action of the radiations emitted by the tracer substances. Thus, the photographic plate gives a visible representation of the distribution of the labeled atoms in sections or slices which have been placed on the radiosensitive emulsion.

The method is not new, as the principles were recognized and used forty years ago by Mügge<sup>5</sup> to locate, topographically, radioactivity in minerals. About twenty years later, Lacassagne, Lattès and Lavedan<sup>6</sup> studied the deposition of a naturally occurring radioelement (polonium) in renal tissue of the rabbit. In the last ten years, after radioisotopes of elements which occur normally in tissues were made artificially, the method has been employed to investigate (histologically) the localization of radioactive iodine in the thyroid, phosphorus in lymph glands and strontium in bone. These radioactive isotopes have a relatively long half-life (as compared with the 14.8 hours of Na<sup>24</sup>) and are deposited preferentially in the tissues in which radioautographs have been obtained. Hamilton, Soley and Eichorn<sup>7</sup> produced many excellent autographs of radioiodine in the thyroid by fastening the tissue section (temporarily) very close to the photographic plate. Permanent alinement of tissue and autograph was obtained by Belanger and Leblond,<sup>8</sup> in coating the tissue with emulsion removed from a photo-

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5. Mügge, O.: Radioaktivität und pleochroitische Höfe, *Zentralbl. f. Min., Geol. u. Paleont.*, 1909, pp. 65, 113 and 142.

6. Lacassagne, A., and Lattès, J.: Mise en évidence par l'autoradiographie des organes, des localisations histologiques du polonium injecté dans l'organisme, *Bull. d'histol. appliq. à la physiol.* **1**:279-283, 1924. Lacassagne, A.; Lattès, J., and Lavedan, J.: Étude expérimentale des effets biologiques du polonium introduit dans l'organisme, *J. de radiol. et d'électrol.* **9**:1-14, 1925.

7. Hamilton, J. G.; Soley, M. H., and Eichorn, K. B.: Deposition of Radioactive Iodine in Human Thyroid Tissue, *Univ. California Publ., Pharmacol.* (no. 28) **1**:339-368, 1940.

8. Leblond, C. P.: Locating Iodine in Tissues Autographically Especially After Fixation by Freezing and Drying, *Stain Technol.* **18**:159-164 (Oct.) 1943. Belanger, L. F., and Leblond, C. P.: A Method for Locating Radioactive Elements in Tissues by Covering Histological Sections with a Photographic Emulsion, *Endocrinology* **39**:8-13 (July) 1946. Leblond, C. P.; Percival, W. L., and Gross, J.: Autographic Localization of Radio-Iodine in Stained Sections of Thyroid Gland by Coating with Photographic Emulsion, *Proc. Soc. Exper. Biol. & Med.* **67**:74-76 (Jan.) 1948.

a dog and a monkey were given similar injections to determine whether any species difference could be noted. In this series of experiments the gross method of autoradiography with frozen slices was used. When the paraffin section technic was tried, the relatively small amount of radiosodium in the preparations was apparently lost prior to embedding, so that no photographic effect was produced.

*Results*—At the earliest interval, of thirty minutes, the radioactive material appeared in the rabbit's eyes predominantly in the region of the ciliary body, choroid and optic nerve, as interpreted by the maxima of darkening of the film emulsion. From the region of the

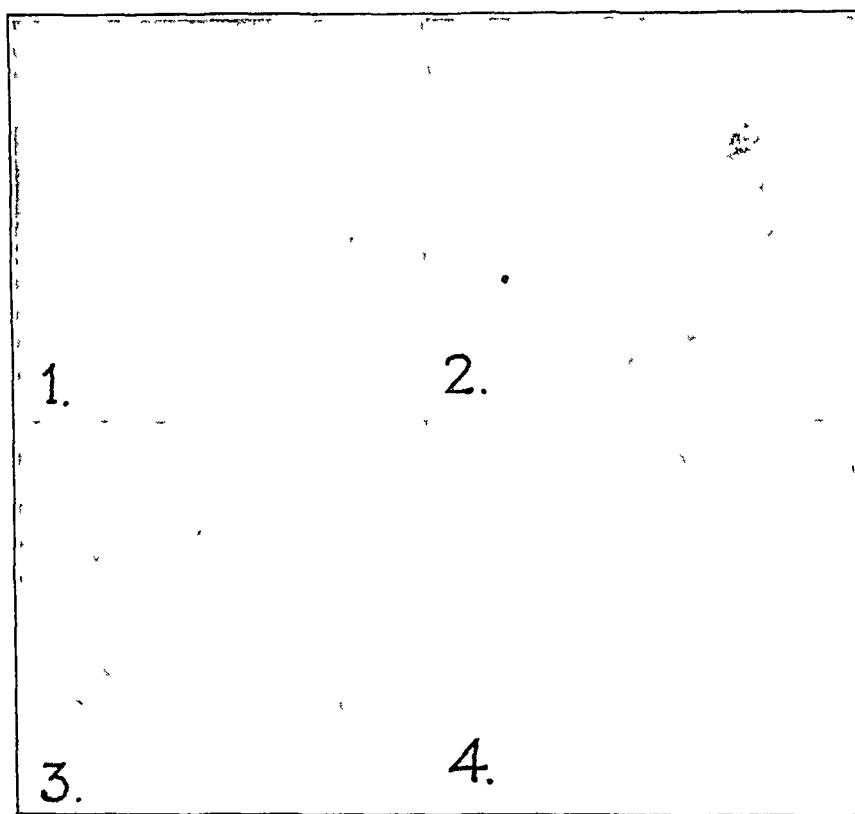


Fig. 1.—Radioautographs of rabbit eyes (1) thirty minutes, (2) one hour, (3) two hours and (4) four hours after intraperitoneal injection of radioactive sodium, 0.6 to 0.8 millicurie per kilogram of body weight.

ciliary body the tracer element permeated the vitreous at its base. Another, less marked, accumulation of radioactive sodium was indicated on the film at the posterior part of the vitreous, in front of the optic nerve. These two localities represented the main portal of entry of the labeled ions into the vitreous, whereas the spreading of radioactive sodium from the choroid through the retina was of a lower degree (fig. 1).

So far as the anterior segment of the eye was concerned, autoradiographs of the early stages suggested that in the rabbit eye the tagged sodium diffused after passing through the walls of the ciliary

injection of an overdose of sodium pentobarbital. Death occurred after a few seconds, and the eyes were enucleated with as little trauma as possible. They were rinsed in isotonic sodium chloride solution U.S.P. and frozen by being embedded in solid carbon dioxide U.S.P. for five minutes and in a freezing mixture of dry ice<sup>®</sup> and alcohol for an additional five minutes. The frozen globes were bisected meridionally with chilled razor blades and microtome knives. By cutting a broad calotte from each half, two slices were obtained which measured in thickness between 1.5 and 2.5 mm., and their surfaces were made smooth by paring. The slices were cut by hand as evenly as possible. Care was taken to maintain the tissue in the frozen state during the preparation of the slices. For photographic exposure, each preparation was placed in an individual paraffin-lined container, which held the slice in close apposition with the sensitive film (Kodak dental x-ray film ultraspeed<sup>®</sup>). The latter was protected by a single layer of cellophane. Here, again, precaution was taken to prevent any, even superficial, melting of the frozen slices. For this purpose, the containers were kept for the period of film exposure in a "deep freeze" chest. When radiosodium had been given by systemic injection, the films were exposed for forty-eight hours. After local administration of the tracer material, the time of exposure was adjusted to the expected amount of radiation from  $\text{Na}^{24}$  in the preparation. The procedures of developing, fixing, washing and drying were the same as those applied in the preparation of thin paraffin sections. In most instances the slices were photographed to permit comparison of anatomic details with the radioautograph.

The radioactive sodium was produced in the cyclotron at Columbia University (department of physics) and arrived at the laboratory as a very dilute (approximately 0.01 per cent) solution of sodium chloride. The radioisotope represented only a small part of the total sodium content. A volume of the solution, containing the desired amount of radioactivity, was evaporated to dryness and later redissolved to a final concentration approximately that of isotonic solution of sodium chloride.

Preliminary experiments were carried out on the photographic effect of agar disks containing a measured amount of  $\text{Na}^{24}$ . Disks 11 mm. in diameter and 1.5 or 3 mm. in thickness, containing 0.1 microcurie, produced a moderate darkening of the (dental x-ray) film, which had been exposed for forty-eight hours and developed in Kodak Developer D-11 for two minutes. A disk of plain agar (1.5 mm. thick) between the film surface and the radioactive disk almost completely prevented the photographic effect under similar conditions of exposure. This was also the case when the amount of the  $\text{Na}^{24}$  in the superimposed disk was tripled and the thickness of the interposed layer of nonradioactive agar was changed to 2.5 mm. The placing of a layer of cellophane between the radioactive material and the photographic emulsion did not appreciably influence the intensity and sharpness of the autograph. It is planned to report, in a later paper, the quantitative values of film darkening by agar disks of different degrees of radioactivity under standard conditions.

#### ENTRANCE OF RADIOSODIUM INTO OCULAR FLUIDS FROM THE BLOOD

*Technic.*—Intraperitoneal injection of a solution containing radiosodium was selected as a general route. The technic of Kinsey, Grant, Cogan, Livingood and Curtis<sup>1</sup> was followed in that radioactive sodium was dissolved in 5 cc. of isotonic sodium chloride solution. The amount of the artificial radioactive element injected, expressed in terms of radioactivity, varied between 0.6 and 0.8 millicurie per kilogram of body weight. The intervals between injection and enucleation were 30 minutes, 1 hour, 2 hours and 4 hours, respectively. The study was carried out on 8 chinchilla rabbits, which averaged 2.5 Kg. in weight. Two cats,

epithelium with this technic, the metabolic inhibitor was administered twenty minutes prior to the intraperitoneal injection of radioactive sodium, and the experiments were terminated after one or two hours. Introduction of cyanide into the anterior part of the eye resulted in a notable increase in the protein permeability of capillaries of the ciliary region. Therefore, in the control eyes, a similar effect on these capillaries was produced with histamine iontophoresis, which has been shown not to interfere with the action of the cytochrome oxidase. Histamine dihydrochloride (0.1 per cent) was used, the electric field being applied with the anode on the eye for two and one-half minutes at 1 milliampere. The experiment was repeated five times.

Although the radioautographs of both eyes showed similarity in the general distribution of the radioactive sodium, a somewhat circumscribed and much denser darkening of the film was observed

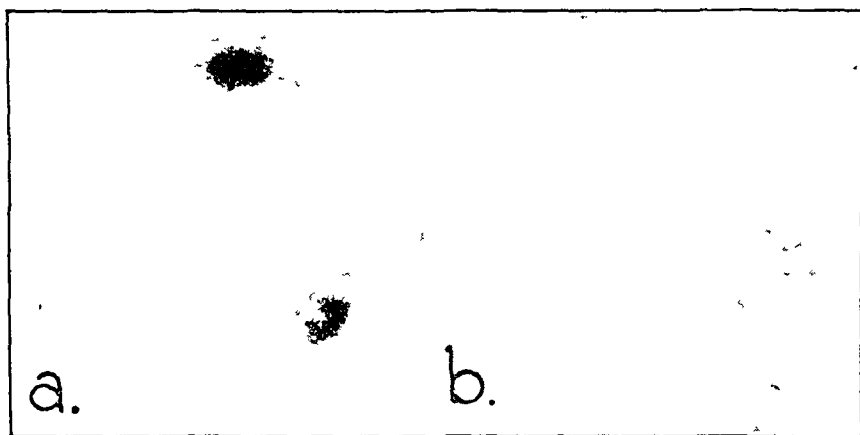


Fig. 3.—Radioautographs of rabbit eyes one hour after intraperitoneal injection of radiosodium: (a) eye pretreated with cyanide and (b) eye pretreated with histamine by iontophoresis.

in the area corresponding to the ciliary body in the slices of eyes treated with the metabolic poison (fig. 3). Hence, there was suggestive evidence in the radioautographs that the inhibition of the secretory mechanism by cyanide resulted in accumulation of the tracer element in the region of the ciliary body.

*Comment.*—In previous experiments<sup>11</sup> with the dye T-1824 on eyes with increased permeability of the capillaries, the movement of the dye-albumin complex was followed. It was concluded that in the early phase, after intravenous injection of the dye, the colored material passed through the walls of the ciliary capillaries into the tissue interstices of the ciliary processes, and from there into the iris and the aqueous

11. von Sallmann, L., and Dillon, B.: The Effect of Diisopropyl Fluorophosphate on the Capillaries of the Anterior Segment of the Eye in Rabbits, *Am. J. Ophth.* 30:1244-1262 (Oct.) 1947.



capillaries into the extracellular fluid of the processes and of the iris, entering chiefly by this route the aqueous in the anterior chamber. The degree to which the capillaries of the iris participated in the passage of labeled sodium from blood to aqueous humor could not be determined. In the few experiments on the dog (2 eyes), the cat (4 eyes) and the monkey (2 eyes), the observations were made one hour after injection of radiosodium, an interval comparable to that for the rabbit; however, the darkening of the area of the ciliary body in films from the dog and the monkey was not so intense as in films from the rabbit. In the experiments on the cat there was no difference between the darkening of the region of the ciliary body and that of the neighboring areas. In these species, as in rabbits, radioactive sodium entered the vitreous predominantly at its base and in the area Martegiani (fig. 2).

A second possible mechanism, that is, active transfer of the tracer across the barrier of the ciliary epithelium into the posterior chamber,

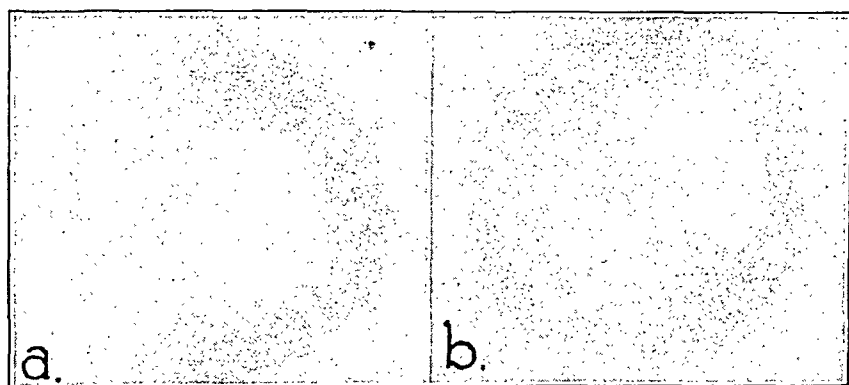


Fig. 2.—Radioautographs of (a) cat eye and (b) dog eye one hour after intra-peritoneal injection of radiosodium, 0.6 to 0.8 millicurie per kilogram of body weight.

followed by diffusion through the pupil into the anterior chamber, must be considered in the later stages. An attempt was made to procure visible evidence of such a secretory mechanism in the transport of radioactive sodium from blood to the fluids of the eye. The simplest way to distinguish between active transfer or secretion and passive penetration seems to be to cut off by the use of metabolic poisons the source of energy by which this transfer operates. For this purpose, a 0.5 per cent solution of sodium cyanide was introduced into the anterior segment of the eye by iontophoresis from the negative pole (2 milliamperes for five minutes). On the basis of previous investigations<sup>10</sup> on the inactivation of the cytochrome oxidase in the ciliary

10. von Sallmann, L.: Controversial Points in Ocular Penicillin Therapy, *Tr. Am. Ophth. Soc.* **45**:570-636, 1947.

radioactive material injected. Fifty eyes were examined in this series. In the group in which diffusion was studied in the enucleated globes, the injection was made immediately after excision, and the globes were suspended in individual moist chambers, kept at 37 C. They were removed in series, at 1, 2, 4 and 6 hours, to be frozen, sliced and used for radioautographs. The control eyes given injections intra vitam were enucleated at the time intervals previously indicated and processed in the usual way. As a rule, from each eye two frozen slices next the meridional plane were available for the radioautographs.

*Results.*—Under the conditions of the experiment, diffusion of the labeled ion in the living eyes was rapid, and, as expected, occurred at a much faster rate than had been observed with penicillin or hemoglobin, studied previously. The radioactive element had apparently diffused through more than two thirds of the vitreous within one hour, but was still unequally distributed after two hours, whereas after four hours the intensity of the darkening of the film was homogeneous in the region corresponding to the vitreous space. With this method, traces of radiosodium could be demonstrated in the aqueous humor one hour after the intravitreal injection. The distribution of the electrolyte in the anterior and in the posterior segment of the eye approached equality at a ten hour interval; later, that is, twelve, eighteen and twenty-four hours after injection, the content of the anterior chamber emitted a moderate amount of radiation, in contrast to the vitreous space, in which the photographic effect of the tracer was still very marked. The region of the ciliary body, and also of the optic nerve, stood out in a few radioautographs as darker areas, suggesting a preferential route of absorption. This observation will be considered later in the experiments on absorption from the vitreous.

In removed globes the radiosodium seemed to diffuse at a lower rate. No relative decrease of darkening of the film in the region corresponding to the anterior chamber was seen at the later intervals when the film was compared with the photographic effect in the area representing the vitreous space. There was no contrasting darkening of the region of the ciliary body, such as was observed in the living eyes.

*Comment.*—It was shown in the experiments with agar disks containing low concentrations of  $\text{Na}^{24}$  that the labeled ion at a distance greater than 1.5 mm. from the film reduced the silver granules to a negligible degree. Therefore, radioautographs of thicker slices of the eye indicated principally the distribution of the radiating atoms within the layers nearest the film surface. This condition, the standardization of the intravitreal injection and of the slicing of the globes and the comparison of the pictures obtained from the two slices in each instance, permitted evaluation of the speed of diffusion of the radiosodium within the cavities of the eye. However, intravitreal injection of any material, even in minimal quantities or with a minimum of trauma,

humor of the anterior chamber. The capillaries of the iris also were dilated, but obviously did not permit passage of the blue material. It is unlikely that the gradient of permeability between the capillaries of the iris and those of the ciliary body as observed for colloids could exist for crystalloids, since it is thought that the capillary walls throughout the body allow simple physical diffusion of these substances. It can be assumed, therefore, that the capillaries of the ciliary body, as well as the capillaries of the iris, permit the movement of radiosodium from the blood to the fluids of the eye.

Kinsey and Grant<sup>12</sup> calculated by mathematical formulation and integration of their experimental results that radioactive sodium and other monovalent cations enter the anterior chamber as a result of a secretory process; that is, their experimental findings were incompatible with the hypothesis of pure ultrafiltration or dialysis. The difference between the radioautographs of cyanide-treated eyes and those of histamine-treated eyes suggested that the process of active transfer was operative in the entry of radiosodium from blood to aqueous humor across the barrier membranes of the ciliary body, thus lending support to the concept of Kinsey and Grant. However, alternative explanations must be considered. It is possible that cyanide increased the permeability of ciliary capillaries more than did histamine, although the protein content of the aqueous humor was similarly raised by the iontophoretic introduction of each of these substances. On the other hand, the absence of a pronounced radioautographic effect at the region of the ciliary body in the histamine-treated eyes may have been induced by a more pronounced action of the drug on the capillaries of the iris.

#### DIFFUSION OF RADIOSODIUM IN THE EYE AFTER INTRAVITREAL INJECTION

*Technic.*—Radioactive sodium was introduced directly into the vitreous (1) to compare the diffusion of the tracer element in the vitreous of the living eye and in the enucleated globe, and (2) to reinvestigate the problem of resorption of electrolytes from the vitreous by the columnar epithelium of the pars plana of the ciliary body.

The radioactive sodium was injected into the vitreous of rabbits with a 30 gage needle in 0.025 to 0.06 cc. of fluid with the eye under local anesthesia. The amount of radiosodium, expressed in terms of radioactivity, ranged from 10 to 60 microcuries, with the higher dose occasionally administered. A needle 1 cm. in length was inserted beneath the superior rectus muscle about 6 mm. behind the limbus. It was directed toward the posterior pole of the eye. The eyes were removed at intervals of 1, 2, 3, 4, 6, 8, 10, 12, 18 and 24 hours. After enucleation, the eyes were frozen, sliced and used for radioautographs, as described in the first part of the paper. Film exposure times varied in accordance with the amount of

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12. Kinsey, V. E., and Grant, W. M.: The Mechanism of Aqueous Humor Formation Inferred from Chemical Studies on Blood-Aqueous Humor Dynamics, *J. Gen. Physiol.* 26:131-149 (Nov.) 1942.

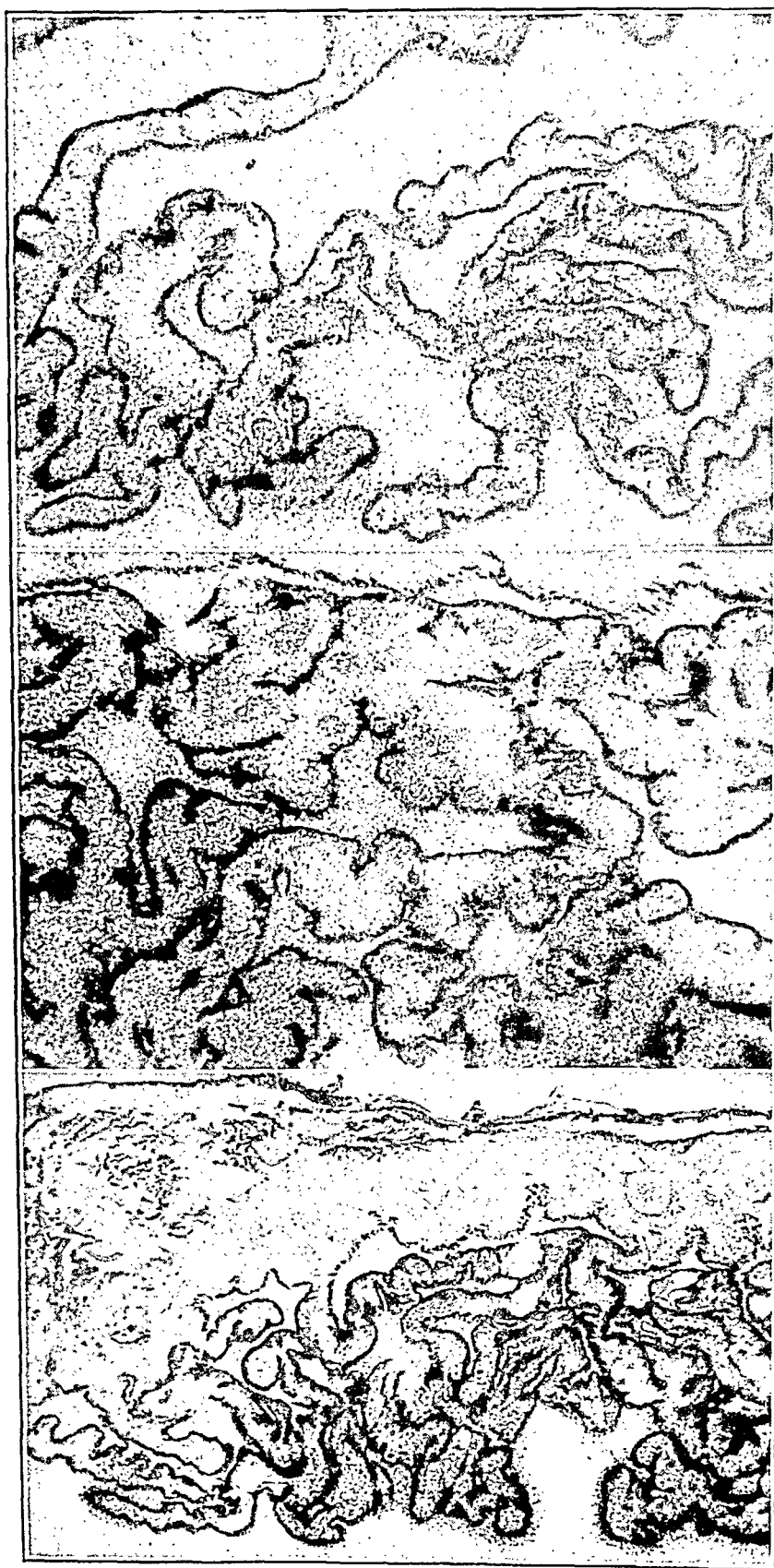


Fig. 4.—Radioautographs of sections of the ciliary body from rabbit eyes two hours after intravitreal injection of radiosodium, 100 to 300 microcuries.

necessarily disturbs physiologic equilibriums. It was for this reason that the data on the living and on the removed eye had significance only in a relative sense. The faster disappearance of sodium from the anterior chamber of the living eyes than from that of the enucleated globes, in contrast to the behavior of the tracer in the vitreous space, favors the theory of a through and through circulation of the tracer. A net loss of sodium by molecular exchange between the fluids and the circulating blood could hardly explain the differences in the radioautographs of the later stages in the two sets of experiments.

#### REABSORPTION OF RADIOSODIUM FROM THE VITREOUS

Studies on reabsorption by the ciliary body have been variously reported in the old and the recent literature. Meller,<sup>13</sup> many years ago, described an occasionally intensive phagocytic and cytolytic activity of the epithelium of the pars plana on red cells in the vitreous. Recently, he found morphologic signs and color reactions in sections of human eyes which convinced him that the columnar epithelium at the base of the vitreous plays an important part in reabsorption of fluid and electrolytes from the posterior part of the eye. Meller<sup>14</sup> and his pupil Lekhraj<sup>15</sup> saw in the histopathologic signs an expression of a physiologic function of this epithelium. Ma and Pillat<sup>16</sup> expressed agreement with Meller's opinion, when they reported that india ink, soluble iron salts, cod liver oil and blood could be demonstrated within the ciliary epithelium two hours after injection of the substances into the vitreous of albino rabbits. No emphasis was placed on the epithelium of the pars plana in bringing about this accumulation of the test substances. On the basis of these observations and those of Friedenwald and Stiehler<sup>17</sup> on the permeability of the ciliary epithelium for certain dyestuffs, experiments with radioactive sodium were conducted in the present series on rabbits, although the pars plana of the ciliary body is not well developed in this experimental animal.

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13. Meller, J.: The Significance of the Ciliary Epithelium in the Absorption of Vitreous Hemorrhages, *Arch. Ophth.* **57**:134-146 (March) 1928; Ueber die Tätigkeit des Ziliarkörperepithels bei der Aufsaugung von Glaskörperblutungen, *Ztschr. f. Augenh.* **69**:113-117 (Sept.) 1929.

14. Meller, J.: Die Quellung der Ziliarepithelien als Ausdruck ihrer resorptiven Tätigkeit bei Behinderung des Abflusses, *Arch. f. Ophth.* **143**:360-388, 1941.

15. Lekhraj, A.: Ueber die aufsaugungende Tätigkeit der Zeller der Ziliarepithels, *Arch. f. Ophth.* **143**:322-331, 1941.

16. Ma, W. C., and Pillat, A.: A Study of the Function of the Columnar Epithelium of the Ciliary Body of Albino Rabbits, *Chinese J. Physiol.* **3**:363-370 (Oct.) 1929.

17. Friedenwald, J. S., and Stiehler, R. D.: Circulation of the Aqueous: VII. A Mechanism of Secretion of the Intraocular Fluid, *Arch. Ophth.* **20**:761-786 (Nov.) 1938.

of movement against a concentration gradient or of the presence of a special driving force. Nevertheless, a few positive results observed with the thick slice technic on living eyes, in contrast to removed globes, suggests such a mechanism.

It was pointed out in the previous paragraph that the trauma of the injection places evaluation of such experiments on uncertain grounds. Furthermore, a biologic radiation effect must be considered possible in view of the relatively high dose of the radioactive element which had been introduced into the vitreous. For this reason, it seems premature to draw final conclusions from the observed phenomena and to bring them in line with Friedenwald's concept of ion transport by a mechanism of oxidation reduction. Kinsey and Grant showed that an apparent active secretion of ions of positive and negative charges may take place as a result of electric attraction of the secreted ions of positive charge for those of opposite charge, to maintain electrical equilibrium. A similar explanation could be adopted for a transfer from within out if Friedenwald's theory of ion transfer by secretion is accepted. An alternative explanation could be based on the hypothesis of Meller and co-workers that the columnar epithelium of the pars plana differs not only morphologically but functionally from the epithelium of the ciliary processes. No direct support for this theory was provided by the radioautographs or by the experiments of Friedenwald in which the selective permeability of the ciliary membranes for acidic and basic dyestuffs was described.

#### IONTOPHORETIC TRANSPORT OF RADIOSODIUM

In the last part of the study, radiosodium was used as a means to demonstrate movement of the substance in the eye under the influence of an impressed electric potential. The experiments were designed to follow the distribution of the tracer without inconvenient sampling errors, which are unavoidable in quantitative determinations of any substances in the vitreous humor.

*Technic.*—The electric field was applied in the form of (1) corneal iontophoresis, with the anode or the cathode on the eye; (2) iontophoresis of the ciliary body, in which the annular zone between the limbus and the ora serrata was used as the portal of entry for the galvanic current (a special applicator tube was made for this purpose); (3) corneal iontophoresis with an isotonic solution of sodium chloride used as electrolyte after the retrobulbar injection of 0.5 cc. of a solution containing radiosodium. Such a technic was described by Leopold<sup>18</sup> as useful in obtaining effective levels of streptomycin in the vitreous.

As a rule, a current of 2 milliamperes was applied for five minutes, and the eyes were removed for radioautography two to four hours after treatment. For

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18. Leopold, I. H.; Wiley, M., and Dennis, R.: Vitreous Infections and Streptomycin: Experimental Studies, *Am. J. Ophth.* 30:1345-1352 (Nov.) 1947.

*Technic.*—The technic of intravitreal injection was the same as that in the diffusion experiments, but the dose of the radiosodium introduced was increased to a range of 50 to 300 microcuries. Both the microscopic method of Evans, with thin paraffin sections, and the thick slice technic were employed. The globes were removed after 1, 2, 3 and 6 hours. Sections were placed on films for forty-eight hours or longer and slices for two hours or less.

*Results.*—The radioautographed sections showed occasionally a conspicuous accumulation of reduced silver grains in and around the ciliary processes, whereas the iris and retina did not contain more than a small number of background granules (fig. 4). With 1 exception, there was no indication that the epithelium of the pars plana was involved in the passage of the tracer into the tissue of the ciliary processes. In this 1 instance a moderate accumulation of reduced silver granules was noted in the loose tissue underlying the columnar epithelium of the pars plana. In a few radioautographs from thick slices the film presented considerably more intense darkening of the area which corresponded to the region of the ciliary body than of the anterior half of the vitreous space (fig. 5). This distribution was



Fig. 5.—Radioautograph of the anterior segment of the rabbit eye four hours after intravitreal injection of radiosodium, 40 microcuries.

not observed when the tracer material had been injected into the vitreous of enucleated eyes.

*Comment.*—Great precaution must be observed in interpreting these results. In the technic with thin paraffin sections the passing of the tissue through two or three changes of acetone or absolute alcohol and xylene washes out most of the sodium, and the subsequent complicated steps of the procedure in the darkroom may account for further loss of the tagged ions. This could explain why in many instances no radiation was demonstrated in any of the sections of a preparation. It is possible, therefore, that in the preparations with the photographically demonstrated accumulation of the tracer within the ciliary processes the radioactive substance had not entered these structures preferentially but, for unknown reasons, was not washed out from the ciliary processes to the same degree as from the iris or parts of the posterior segment of the eye. Since almost all radiosodium was removed during dehydration from the vitreous space, it could not be decided from the sections whether the accumulation of  $\text{Na}^{24}$  in the ciliary processes exceeded that at the base of the vitreous, that is, whether there was an indication

electrode that true ion transfer took place and that diffusion of the undissociated salt through damaged epithelium played a minor part.

In aphakic eyes of rabbits, radiosodium was shown to diffuse from the anterior chamber into the vitreous when it had been introduced by corneal iontophoresis with the anode as the active electrode. The darkened area of the film occupied two hours after treatment a roughly triangular space in the middle third of the vitreous. If the interval between the application and the removal of the eye was prolonged to four hours, a moderate darkening of the film was equally distributed throughout the vitreous space. Total retinal detachment, which was present in the preparations of one aphakic eye, caused only a faintly discernible difference in the darkening of the film between the area corresponding to the vitreous body and that corresponding to the retro-retinal space.

In general iontophoresis of the ciliary body did not produce easily demonstrable quantities of radiosodium in the vitreous space. Several times a faint darkening of the film was noted in a narrow zone of the peripheral region of this space. Exceptionally, radioautographs showed an intense darkening of the film in the area of the vitreous body of normal rabbit eyes with the lens in place. This darkening increased toward the posterior pole and the optic nerve. In the majority of experiments the radioactive element seemed to be accumulated in the anterior chamber, similar to the results accomplished with corneal iontophoresis. Changes in the design of the applicator tube, modification in the technic and the preceding use of vasoconstrictors have failed so far to reveal the cause of the irregularities of the results and to render the method reliable in producing appreciable sodium levels in the vitreous space.

Application of the electric field according to the method of Leopold in order to increase penetration of the tracer from Tenon's space into the posterior part of the eye was ineffective under the conditions of the experiment. A simultaneous use of vasoconstrictors did not influence the results.

*Comment.*—It was known from the work on penetration of antibiotics that corneal iontophoresis provided high concentrations of these test substances in the anterior segment of the eye. Radioautographs obtained with the use of  $\text{Na}^{24}$  confirmed these observations and demonstrated that the accumulation of the diffusible ion was practically confined to the area of the anterior chamber. The nature of the penetration as being essentially a true ion transport was indicated in the negative results when the pole on the eye was reversed.

The permeation of radiosodium from the anterior chamber into the vitreous in aphakic rabbit eyes could be well followed in the radioautographs. These observations emphasize the feasibility of introducing



all experiments a quantity of sodium chloride which contained the radiosodium was dissolved in distilled water to furnish an activity of 100 microcuries per cubic centimeter of solution. Twenty rabbit eyes were used in this series.

*Results* (fig. 6).—Corneal iontophoresis with the anode on the eye resulted in a high concentration of the labeled ion in the anterior

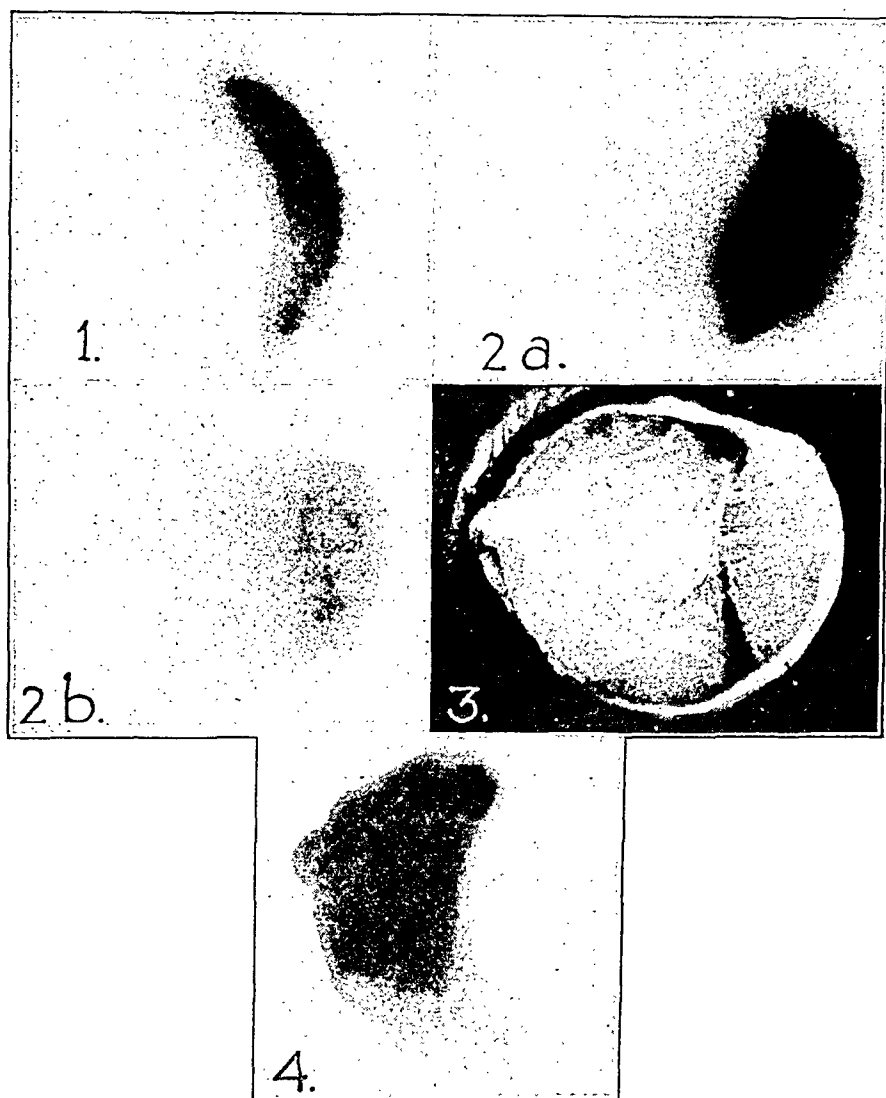


Fig. 6.—Radioautographs (1) of the normal rabbit eye two hours after corneal iontophoresis with radiosodium, (2) of aphakic rabbit eyes (a) two hours and (b) four hours after corneal iontophoresis with radiosodium; (3) aphakic rabbit eye; (4) Radioautograph of normal rabbit eye two hours after iontophoresis of ciliary body with radiosodium.

chamber. This accumulation of the tracer was limited almost exclusively to this part of the normal rabbit eye. When the terminals were reversed and the cathode was used as the active electrode, scarcely any penetration was noticed on the film. It is evident with anode as the

# TREATMENT OF PEDICULOSIS CILIARIS WITH ANTICHOLINESTERASE AGENTS

Report of a Case

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AND

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NEW DRUGS for the treatment of pediculosis ciliaris cannot be said to be especially needed. The time-honored ammoniated mercury has proved itself effective when used liberally enough. Yet it is of considerable interest, and may be of some practical usefulness, to know that the common physostigmine in the standard concentrations used for the treatment of glaucoma is just as effective as ammoniated mercury, if not more so. Tetraethylpyrophosphate, and presumably many other anticholinesterase compounds, are also effective.

A case in which we had an opportunity to study the effect of physostigmine and tetraethylpyrophosphate is reported.

## REPORT OF CASE

E. B., a woman aged 49, during routine refraction, was noted to have blepharitis. In reply to questioning, she stated she had had severe itching of the lids, especially at night. Gross examination showed black discoloration of the eyelashes and loose, tiny black dots on the cheeks below the lashes. The first impression was that of eyelash dye caked on the lashes. Examination with the slit lamp, however, showed that the discoloration was due to 100 to 200 nits adherent to the ciliary shafts of each upper lid and 20 to 40 nits on the shafts of each lower lid. Usually there were several of these nits to each hair shaft. The nit consisted of a chitinous case shaped like a cornucopia, with the large orifice facing outward. Approximately one tenth of the cases were empty. Less obvious were 5 to 7 adult pediculi on each upper lid and 1 to 3 pediculi on each lower lid. These parasites were partly embedded, head foremost, in the skin of the margin of the lid, with the posterior, clawlike legs in contact with the base of the cilia. The legs showed spontaneous movements most of the time. Characteristic were eight to ten brown dots arranged symmetrically on the back of each pediculus. The pediculi were transparent but contained pulsatile viscera with a reddish black content, which was presumed to be ingested blood. These contents were intermittently excreted, and the excreta comprised the black dots seen grossly on the patient's cheeks.

Nits were also found in the pubic area and the axillas, but none on the scalp. There was no preauricular or cervical lymphadenopathy.

To determine what effect anticholinesterase agents would have on the pediculi, tetraethylpyrophosphate and physostigmine were selected, since the dose of

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antibiotics by corneal iontophoresis in infections of the posterior part of aphakic eyes.

Judged from the radioautographs, no iontophoretic method was found which provided a reasonably consistent level of the radioactive isotope in the vitreous of rabbit eyes with the lens in place. Iontophoresis of the ciliary body gave erratic results, and with the technic used the properly applied electric field after retrobulbar injection of the tracer material was disappointing.

#### SUMMARY AND CONCLUSIONS

1. Radioautographic technics were applied to studies of the movement of  $\text{Na}^{24}$  in the eye, a gross method being used for frozen slices and the microscopic method of Evans for thin paraffin sections of the eye.

2. Phases in the penetration of the tracer substance from the blood into the fluids of the eye were made visible. The regions of the ciliary body and of the optic nerve were shown as the main portals of entry. Diffusion through the capillary walls was found to be the predominant factor in this process.

3. Cyanide as a specific inhibitor of energy-providing reactions was employed to determine the existence of a second factor operative in the transport of  $\text{Na}^{24}$  from blood to the eye, that is, of active transfer by the barrier membranes of the ciliary processes. There was suggestive evidence that such a mechanism operates in the movement of sodium across the barrier membranes of the ciliary body.

4. Diffusion of  $\text{Na}^{24}$  in the vitreous and into the anterior chamber occurred at a rapid rate after intravitreal injection of the tracer. Its movement in the living eye exceeded that in the enucleated globe. Comparison of the radioautographs in the two sets of experiments supports the theory of through and through circulation of the tracer ion in the living eye.

5. The problem of absorption of electrolytes by the ciliary body was studied with  $\text{Na}^{24}$ , both methods of radioautography being used. A conspicuous accumulation of the tracer was observed in the ciliary processes after intravitreal injection, but no final conclusions could be drawn with regard to the nature of this phenomenon.

6. The influence of an applied electric field on the movement of  $\text{Na}^{24}$  in the eye was made visible by radioautography. Various types of iontophoresis were studied. None of them was suitable for the introduction of regularly substantial quantities of the tracer into the vitreous space, even though such technics did demonstrate appreciable penetration into the anterior chamber of normal eyes and into the vitreous space of aphakic eyes.

## INTRAVITREAL USE OF STREPTOMYCIN

ROBERT E. SHOEMAKER, M.D.

ALLENTOWN, PA.

EXPERIMENTAL studies concerning the use of streptomycin in treatment of intraocular infections have been published.<sup>1</sup> Since, as has been shown by Leopold and Nichols,<sup>1a</sup> streptomycin penetrates poorly from the blood stream into the normal vitreous humor, systemic administration of the drug is inadequate in therapy of infections of the vitreous. In a more recent series of experiments,<sup>1b</sup> Leopold demonstrated that streptomycin given by direct intravitreal, retrobulbar injection plus iontophoresis, or by irrigations of the anterior chamber reduced the severity of experimental infections of the vitreous due to *Escherichia coli*. These methods were effective in the order noted. The report further indicated that direct intravitreal injections of streptomycin produced retinochoroidal exudation and subsequent degeneration, but that in concentrations below 800 micrograms per injection the damage was minimal and was limited to the site of injection. Studies of retention of streptomycin in the vitreous<sup>1c</sup> indicated that after a single intraocular injection of 100 micrograms of the drug an adequate therapeutic concentration may be expected for over twenty-four hours.

That such experimental studies are of great clinical value is demonstrated by the following case, which is of particular interest because of the severity of the infection and the apparent sight-saving response to direct intravitreal injection of streptomycin.

### REPORT OF A CASE

B. S., a Negro aged 26, was admitted to the Allentown General Hospital July 14, 1947, after injury from an accidental dynamite explosion while he was drilling a hole in rock preparatory to blasting.

Examination revealed that vision was clear in the right eye (i. e., when examined in the accident ward, the patient said he could see normally; no tests with Snellen notation were attempted) and was limited to light perception in the left eye. Both lids were swollen and showed numerous areas of penetration of rock dirt. The right eye showed a perforating wound of the cornea with a prolapse of the iris at 5 o'clock near the limbus. The lens and the visible portion of the fundus were clear.

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1. (a) Leopold, I. H., and Nichols, A.: Intraocular Penetration of Streptomycin Following Systemic and Local Administration, *Arch. Ophth.* **35**:33 (Jan.) 1946. (b) Leopold, I. H.; Wiley, M., and Dennis, R.: Vitreous Infections and Streptomycin, *Am. J. Ophth.* **30**:1345, 1947. (c) Bellows, J. G., and Farmer, C. J.: Streptomycin in Ophthalmology, *ibid.* **30**:1215, 1947.

these drugs tolerated by the eye was known. Accordingly, 1 drop of 0.01 per cent tetraethylpyrophosphate in purified kerosene was instilled onto the lids of one eye and 1 drop of purified kerosene without the drug onto the lids of the other eye. Within ten minutes the pediculi on the side on which the tetraethylpyrophosphate was used showed complete cessation of all visceral and limb movements, while the pediculi on the side where kerosene alone was used showed the usual visceral movements and a somewhat increased movement of the limbs. The following day the pediculi which had been exposed to tetraethylpyrophosphate were represented only by flattened carcasses, obviously dead, while those exposed to the control kerosene were normal. The nits appeared unchanged on both sides.

One drop of 0.01 per cent physostigmine base in kerosene was then applied to the lid containing the motile pediculi. No effect was evident on the pediculi, and a drop of 0.1 per cent physostigmine base in peanut oil was then instilled onto the lashes. The only effect observed over a thirty minute period was increased twitching of the limbs. Without further treatment, the patient was reexamined two days later and was found to have one small, presumably young, motile pediculus on each upper lid.

The impression was obtained, therefore, that 1 drop of 0.01 per cent tetraethylpyrophosphate had promptly killed the adult pediculi and that 1 drop of 0.1 per cent physostigmine base killed the adult forms more slowly, but that neither drug had prevented hatching of new pediculi from the nits.

To compare the effect of treatment with physostigmine with that of the usual ammoniated mercury, one eye was treated on two days with single instillations of 2 per cent ammoniated mercury ointment U. S. P. and the other eye with an ointment containing 0.25 per cent physostigmine base in petrolatum. Two days after the last instillation the patient was reexamined. The eye treated with physostigmine showed no adult pediculi, and there appeared to be a greater proportion of evacuated egg cases. The eye treated with ammoniated mercury showed 4 to 5 motile pediculi and no evident change in the nits.

The patient continued the treatment with ammoniated mercury in one eye and with physostigmine in the other. One week later there were no pediculi on either eye; and the nits, although no less in number, appeared somewhat shriveled up, and there was a greater proportion of empty cases. At this stage the pubic and axillary regions were treated by local application of Wyeth's bornate® (5 per cent isobornyl thiocynoacetate and 0.6 per cent of dioctyle sodium sulfo-succinate). No further treatment was given the eyes.

The patient was reexamined two weeks and four weeks, respectively, after discontinuing treatment. The nits decreased in number spontaneously, and at the last visit the few remaining egg cases were all empty.

The patient's daughter, who, incidentally, slept with the patient, was examined on two occasions. At the first examination no pediculi or nits were seen. At a later examination a single pediculus and a single nit were found. These disappeared with the instillation of physostigmine ointment.

#### SUMMARY

The anticholinesterase drugs, tetraethylpyrophosphate (0.01 per cent in purified kerosene) and physostigmine ointment (0.25 per cent physostigmine base in petrolatum) were effective in the treatment of pediculosis ciliaris.

The patient was discharged from the hospital on August 9, to the care of Dr. George Dublin, at Wills Hospital, Philadelphia. The eye at this time was almost white; the anterior chamber was grossly clear; the lens was opaque posteriorly, and light perception and projection were good temporally, though impaired nasally.

The subsequent history is briefly summarized: The patient was admitted to Wills Hospital on Aug. 12, 1947, for a series of treatments with artificial fever, induced with intravenous injections of typhoid vaccine. He was discharged one month later and was readmitted October 7, when a linear cataract extraction was done.

The patient was seen again in April 1948. The cornea showed scattered small, punctate scars. The anterior chamber was clear. There was a small surgical coloboma. The eye was aphakic. A narrow, dense white membrane stretched across the center of the pupillary space. Except for a single opaque strand in the retrolental area, the vitreous was clear. The nasal, superior and inferior periphery of the retina appeared normal. Beginning at the somewhat pale disk and extending in a fan-shaped area temporally a gray-white, cobweb-like scar could be seen. The scar tissue appeared to be retinal, covering some of the vessels; in other areas, the vessels coursed over the scar. This scar formation included the macula and a rather large perimacular area.

The patient fixed eccentrically—the eye was held in about 15 degrees of exotropia—and with a + 12 D. lens visual acuity varied from 16/200 to 20/200, according to the searching attempt at fixation.

#### COMMENT

A rather interesting part of the clinical picture was the complete loss of light perception for six days. This may have been the result of acute optic neuritis, either toxic or due to direct bacterial infection of the nerve head itself. At the time of writing, the fundus picture showed a somewhat pale nerve head, partially covered with a strandlike white membrane.

The subsequent retinal degeneration in this case parallels that observed in animal experimentation with streptomycin, except that it was not localized at the site of injection. However, it should be pointed out that a total of 2,300 micrograms of streptomycin was placed in the posterior segment and that the same amount introduced experimentally into animal eyes might cause widespread chorioretinal degeneration.

It is felt that direct intravitreal injection of streptomycin in this case saved one eye after systemic therapy with penicillin had failed. Later bacteriologic reports<sup>4</sup> showed that the infecting organism was a gram-positive, spore-forming bacillus of the *brevis* group. Sensitivity tests<sup>5</sup> showed the organism to be more susceptible to penicillin than to streptomycin *in vitro*. The clinical result stresses the inadequacy of systemic routes of administration for infections of the vitreous humor and the effectiveness of local therapy, even when the antibiotic

4. Morton, H.: Personal communication to the author.

5. Sensitivity tests were made by Mr. R. N. Shoemaker, research fellow in the department of biology, Lehigh University.

The left eye presented a perforating, 2 mm. laceration of the sclera at 4 o'clock about 3 mm. from the limbus. The cornea showed penetration wounds at 4 o'clock about 3 mm. from the limbus, a central perforating wound and a third perforation at 11 o'clock about 2 mm. from the limbus—all the corneal wounds having a prolapse of iris. The anterior chamber was filled with blood.

The patient was placed under treatment with 40,000 units of penicillin every three hours, and tetanus and gas gangrene antitoxin U. S. P. was administered.

The initial surgical treatment, undertaken four hours later, consisted of the following procedures: right eye: excision of the prolapsed iris; left eye: (1) excision of the prolapsed iris, (2) suture of corneal wounds and (3) limbal incision for (a) evacuation of the hyphema and (b) evacuation of loose lenticular material.

The following day the right eye appeared in good condition, with a clear anterior segment, although there was some vitreous haze. The left eye showed an intense inflammatory reaction, with clouding of the aqueous.

On the second postoperative day, July 16, examination of the right eye showed a clear anterior segment, but the vitreous was more turbid and details of the fundus could not be seen; vision was reduced to counting fingers at 3 feet (90 cm.). The left eye showed frank endophthalmitis, with purulent exudate extending through the anterior chamber. The patient was taken to the operating room for the following procedures: (1) irrigation of the anterior chamber of the right eye with penicillin solution (5,000 units per cubic centimeter), and (2) simple enucleation of the left eye with drainage. Cultures of material from the enucleated eye were made.

On July 18, vision in the right eye was reduced to perception of hand motions, the anterior segment and lens continued to be clear, but yellow exudate was grossly visible behind the lens; episcleral injection was becoming pronounced, and the globe was tender. Smears from the enucleated eye revealed no organisms, but the culture was reported as showing a gram-negative bacillus.

Since the response to penicillin was poor, both as given systemically and as injected into the anterior chamber, systemic administration of streptomycin<sup>2</sup> (0.5 Gm. every four hours) was begun, and, at the suggestion of Leopold,<sup>3</sup> approximately 900 micrograms of streptomycin was injected into the vitreous. For the latter, a tuberculin syringe and a 26 gage needle were used, the needle being directed through the pars plana in the upper nasal area.

On the following day, July 19, the clinical appearance was worse, and vision was reduced to vague perception of hand motions. The intravitreal injection was repeated in larger dose (approximately 1,400 micrograms), and a streptomycin pack, containing 20,000 micrograms per cubic centimeter, was placed in the cul-de-sac for one hour.

Four days later, July 23, vision was reduced to nil—the patient did not have light perception. The clinical appearance of the eye remained in status quo except that a cataract could be seen developing, the opacity extending forward from the posterior subcapsular area.

On July 26, six days after the intravitreal injection, the inflammatory reaction was becoming less marked, although there was still absence of light perception. Systemic administration of streptomycin was discontinued.

By July 30, the tenth day after the injection, light perception had returned; the inflammatory reaction of the globe was subsiding, and the lens had become irregularly opaque posteriorly.

2. The streptomycin used was calcium chloride complex.<sup>®</sup>

3. Leopold, I. H.: Personal communication to the author.

# Clinical Notes

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## A SIMPLIFIED PERIMETER OF WALL TYPE

ANTHONY AMBROSE, M.D.  
NEWARK, N. J.

For the simplified wall perimeter which I present I claim nothing original except the idea for the wall suspension.

The wall clamp was taken from an old gynecology table. The supporting bar was made by a blacksmith. Both pieces were chrome plated. The perimeter arm is  $\frac{3}{4}$  inch (1.9 cm.) plywood and is graduated to measure 100 degrees. It was given four coats of jet black paint. I had previously put on four coats of a neutral gray but found that the black paint is much more satisfactory. The point on the end of the arm was a brass cup hook which was straightened out and filed to a point. It points directly on the protractor to the meridian which is being examined. A wooden drawer knob has been screwed onto the back of the arm in order that one may hold it in position by hand in the oblique angles. The protractor is made of the same material and at first was 6 inches (15 cm.) in diameter, but I later found that I had to cut the sides off, as the width prevented the instrument from lying flat against the wall.

The right-angled supporting arm is made of the same plywood as is the T-shaped foot plate, which is adjustable. The end of the supporting bar was flattened, and three holes were drilled in it: One is to accommodate a toggle bolt, which serves to connect the perimeter arm, the protractor and the supporting arm. The latter and the protractor are screwed together by screws placed in the other two holes. The wing of the toggle bolt is screwed into the back of the perimeter arm. The toggle bolt is secured by two washers and a butterfly nut at its very end. The head of the toggle bolt was dipped in flat white paint six times, being dried between each dipping. It serves as a fixation point. I marked the degrees off each side of the arm with raised numbers used for identifying window screens, starting at 10 degrees with no. 1 and ending with 90 degrees with no. 9, the zero point being opposite, on the line of the fixation point.

I first used the perimeter with the protractor fixed to the supporting bar and employed a Bausch & Lomb chin rest, which I use for the tangent screen. I later bought and attached the supporting arm when I was able to secure a Bausch & Lomb chin rest from a Ferree-Rand perimeter. The moving parts are separated from one another by washers from the wheels of roller skates. I use Dr. Berens' test objects attached on dowels 18 inches in length and  $\frac{1}{4}$  inch



used has a lesser degree of antibacterial activity. It may be that immediate intravitreal injection of penicillin or streptomycin, or perhaps, even better, a combination of the two, would have changed the course of events in the left eye.

#### SUMMARY

Intravitreal injection of streptomycin was used clinically in a case of bacterial endophthalmitis and appears to be a safe procedure in cases in which it is indicated. Unfavorable effects on the vitreous were practically nil. Retinal degeneration occurred, as in experimental animals, but one could minimize this by not exceeding the recommended dosage.

1248 Hamilton Street.

(0.63 cm.) in thickness, painted the same black as that of the perimeter. When taking the visual field, I pull down my tangent screen, which is black and offers the same background as the perimeter arm. When the peripheral fields are finished, I move the patient back to 1 meter and use a Bausch & Lomb chin rest, which I have

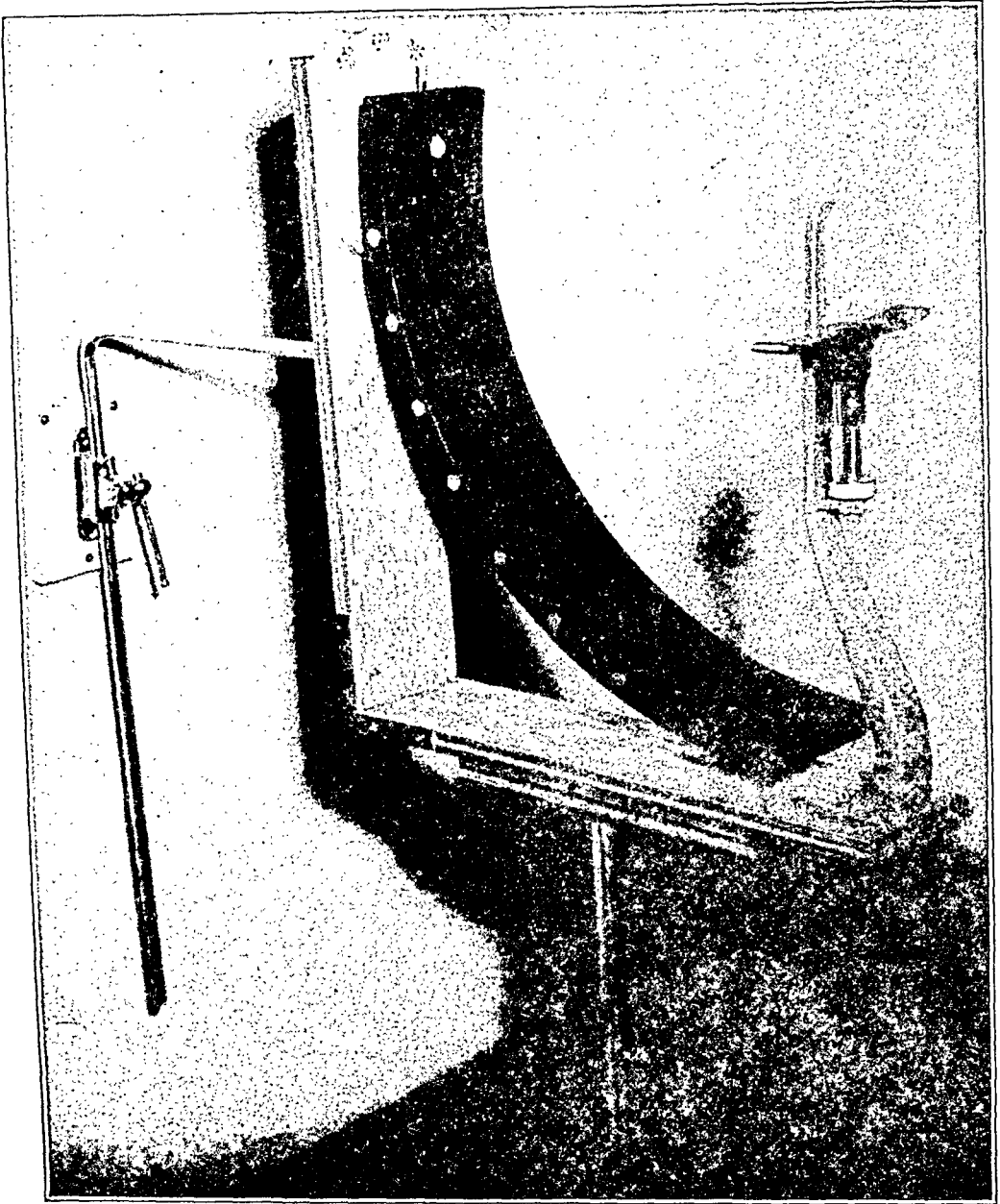


Fig. 3.—Close-up view of the instrument.

on a movable pedestal, in taking the central fields. When the occasion requires it, I also use the Bausch & Lomb stereocampimeter, as shown in the pictures. The lighting is obtained from an overhead lamp, which illuminates the tangent screen. It is a 100 watt daylight bulb, the illumination being augmented from the side by another daylight bulb.

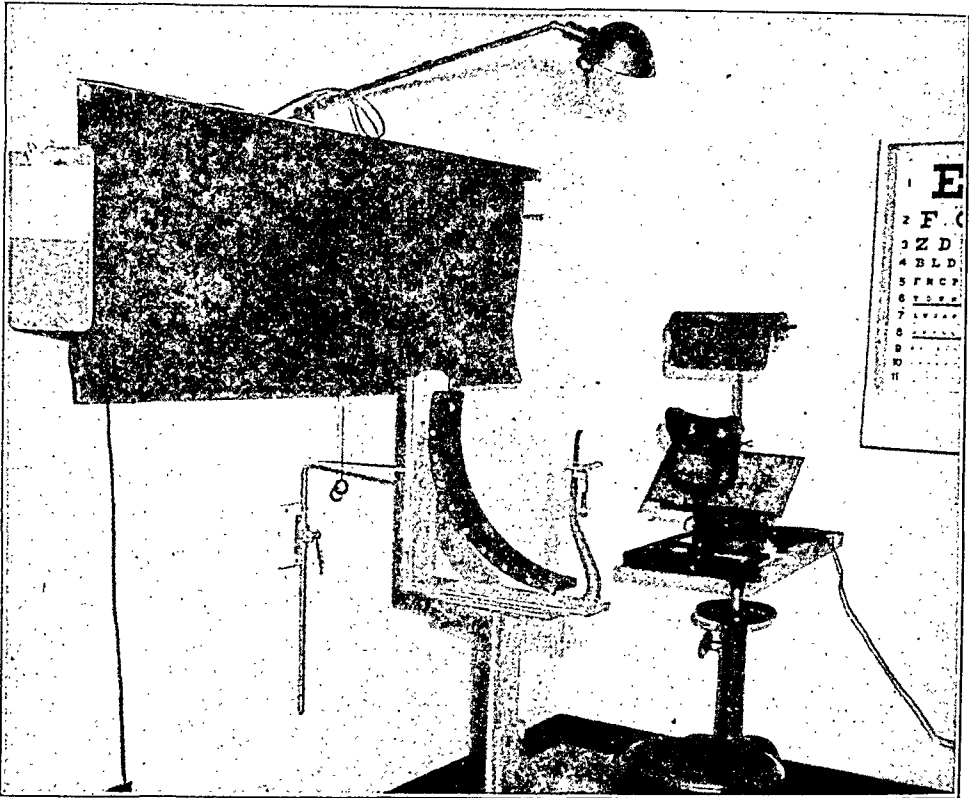


Fig. 1.—Instrument in position of use.

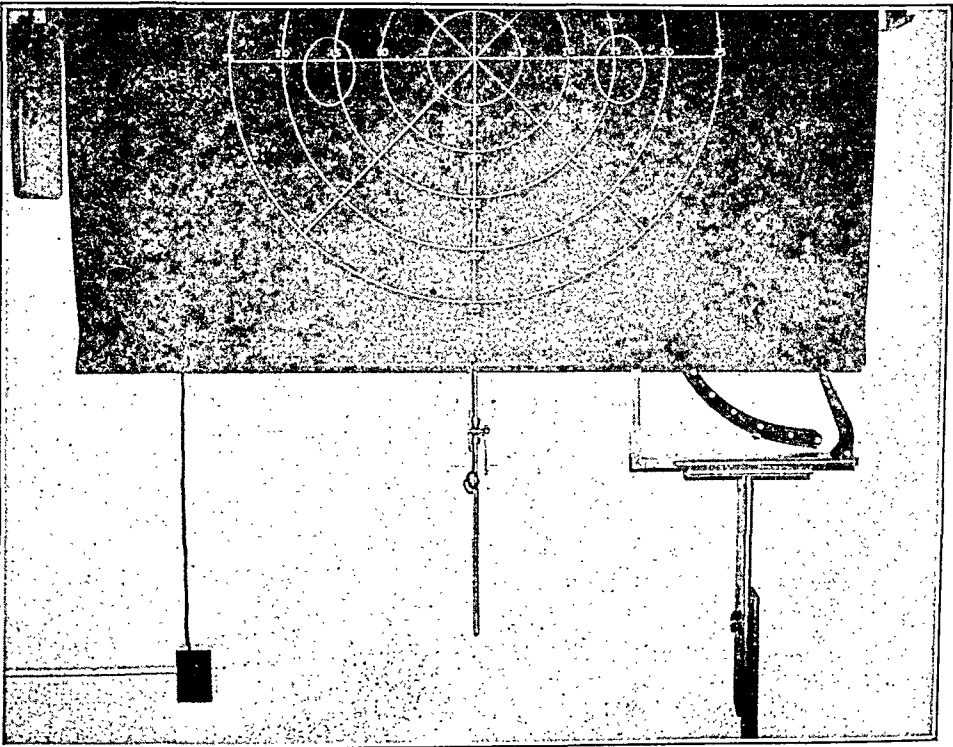


Fig. 2.—Instrument flat against the wall, partly covered by the tangent screen.

# News and Notes

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## GENERAL NEWS

**The American Orthoptic Council.**—The American Orthoptic Council announces the second annual course of instruction for orthoptic technicians. This course consists of two parts, the first, nine weeks of lectures, demonstrations and laboratory work by outstanding ophthalmologists and certified technicians, from June 25 to Aug. 27, 1949, at Nason College, Maine.

This basic instruction will be followed by the second part, which consists of six to twelve months of practical work in clinics and offices, throughout the United States, under the supervision of certified orthoptic technicians. Completion of the full course will qualify the student to take the examinations of the American Orthoptic Council. Further information may be procured from the American Orthoptic Council, 1605 Twenty-Second Street, N.W., Washington 8, D. C.

**Attention Candidates for Board Examinations.**—The American Board of Ophthalmology wishes to announce that it does not evaluate, approve or disapprove any ophthalmic residency toward fulfilling the requirements of candidates for board examinations. Any candidate who qualifies for the board examination and completes the prerequisites as outlined in the booklet of information will be accepted. A copy of this booklet can be obtained from the Secretary of the American Board of Ophthalmology, 56 Ivie Road, Cape Cottage, Maine.

**The Annual deSchweinitz Lecture.**—The Twelfth Annual deSchweinitz Lecture will be given on Thursday, Nov. 17, 1949, by Arthur J. Bedell, M.D., of Albany, N. Y. His subject will be "The Macula in the Aged."

## SOCIETY NEWS

**Annual Congress of the Ophthalmological Society of the United Kingdom.**—The annual congress of the Ophthalmological Society of the United Kingdom was held at the Royal Society of Medicine, 1 Wimpole Street, London, W.1, on March 31 and April 1 and 2, 1949; F. A. Juler, C.V.O., M.B., F. R. C. S., president.

The presidential address, entitled "Some Points in the Operation for Acute Glaucoma" and "Reflections on Refraction," was followed by the presentation of the Bowman medals.

The following papers were presented: "The Technic of Plastic Operations in the Neighborhood of the Orbit," Mr. D. N. Matthews; "Reduction of Intraocular Tension by Curare, Retrobulbar Injection of Procaine and Di-Isopropyl Fluorophosphate," Mr. J. R. Wheeler; "The Problem of Awareness or Nonawareness of Visual Field Defects," and "Cerebral Metamorphopsia," Dr. Macdonald Critchley; "Normal and Pathologic Ocular Pigment," Mr. Eugene Wolfe; "Clinical Estimation

In my opinion, the instrument has many advantages. It is cheap; it can be put behind a door, or even inside a closet. It can be permanently attached by the supporting arm to a wall or a door, and the patient is then adjusted by a revolving stool. It might also be attached to a table by a bolt on the lower supporting arm.

I conceived the idea because my Ferree-Rand perimeter took up more space than was available in the room in which I was using it.

NOTE.—Since the illustrations were made, a floor foot plate, 12 by 4 by 1 inch (30.4 by 10 by 2.5 cm.), was attached to the upright support in order to give the instrument more stability.

15 Washington Street.

# Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

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## Aqueous Humor

PARASYMPATHOMIMETIC EFFECT OF AQUEOUS HUMOR IN HUMAN EYES WITH AND WITHOUT CHRONIC SIMPLE GLAUCOMA. S. BLOOMFIELD, *Proc. Soc. Exper. Biol & Med.* 60: 293, 1943.

The results are presented of the bioassay of aqueous humor from human eyes prepared according to the method applied by Engelhart to animals. In a series of 10 human eyes without glaucoma, every sample of aqueous humor contained a parasympathomimetic substance which, in the 2 cases so tested, was found to be similar to acetylcholine. In the aqueous humor of 7 human eyes with chronic simple glaucoma no such parasympathomimetic substance could be demonstrated.

W. ZENTMAYER.

A NEW METHOD OF MEASURING THE RETINAL BLOOD PRESSURE AS AN OBJECTIVE PROOF OF THE FORMULA OF THE HYDRODYNAMIC EQUILIBRIUM OF THE EYE. A. DASHEVSKY, *Vestnik oftal.* 26: 22, 1947.

In a previous paper Dashevsky described a formula expressing a new law of the adequate reaction of the eye to pressure which is in direct proportion to the difference of the diastolic blood pressure and the true intraocular pressure.

In order to verify the correctness of his formula of the hydrodynamic equilibrium of the eye, Dashevsky succeeded in measuring the diastolic blood pressure in the eye without using the usual tonoscopic method (without increasing the ophthalmotonus to the level of the diastolic pressure or the appearance of the first pulsation of the central retinal artery). The method is an indirect one, which combines the reactivity of the eye, the ophthalmotonus and the blood pressure, and it opens new prospects for experimental work.

This formula combines not only the hydrostatic relationship of the blood pressure, the ophthalmotonus and the physicochemical condition, but also the important nervous component, the changes of which appear as the variations in the reactivity of the eye. The law of the adequate reaction of the eye to its pressure is the result of the mobile, and at the same time stable, condition in the eye which is called hydrodynamic equilibrium.

A table and the explanation of the formula illustrate the article.

O. SITCHEVSKA.

of Pressure in the Retinal Arteries," Dr. E. Hartmann; "Aneurysms of the Internal Carotid Artery," Dr. S. P. Meadows; "Congenital Total Color Blindness, with Otosclerosis and Hypertension as Associated Hereditary Abnormalities," Mr. W. J. Wellwood Ferguson and Dr. Alastair G. MacGregor; "Measurement of the Retrobulbar Resistance (Orbitonometry) in the Clinic," Dr. A. C. Copper; "Clinical Electroretinography," Dr. G. Karpe; "Problems in Ophthalmic Dispensing," Mr. J. Pike; "Retinal Arteriolar Spasm in Toxemia of Pregnancy," Dr. J. Berkson.

A discussion on "Corneal Grafting" was opened by Prof. A. Franceschetti; Mr. J. W. Tudor Thomas; Prof. G. P. Sourdille, Mr. B. W. Rycroft and Mr. D. P. Choyce.

Brief pictorial demonstrations of cases were made.

**Medical Society of the State of New York, Section on Ophthalmology.**—The annual convention of the Medical Society of the State of New York, Section on Ophthalmology, was held May 5 at the Hotel Statler in Buffalo. The chairman of the program was Darrell G. Voorhees, M.D., of New York; the secretary, Walter F. Duggan, M.D., of Utica. The following papers were presented: "Complications and Failures of Retinal Reattachments," by Ivan J. Koenig, M.D., Buffalo; "Functions of the New York State Commission for the Blind," by David F. Gillette, M.D., Syracuse, and "Defects in the Visual Fields Resulting from Increased Intracranial Pressure," by C. Wilbur Rucker, M.D. (by invitation), of Rochester, Minn. Discussions were opened by Loren P. Guy, M.D., New York; David F. Gillette, M.D., Albany, and John F. Gipner, M.D., Rochester.

**Ophthalmology Lectures, Royal College of Surgeons of England.**—The following lectures were delivered at the College, in Lincoln's Inn Fields, London, W.C.2, on March 29 and 30, 1949: "Cataract Associated with Lesions of the Skin," Prof. A. Franceschetti, University of Geneva; "Ophthalmic Aspects of Protein Deficiency and Disordered Protein Metabolism," Prof. G. B. Bietti, Pavia University; "Psychosomatic Symptoms in Ophthalmology," Dr. E. Hartmann, Hôpital Lariboisière, Paris; "Ophthalmic Manifestations of Besnier-Boeck Disease," Prof. H. J. M. Weve, Rijksuniversiteit.

**Oxford Ophthalmological Congress.**—The next meeting of the Oxford Ophthalmological Congress will be held in Oxford, England, July 7 to 9, 1949. The Doyne Memorial Lecture will be delivered at this meeting by Professor Goldman, of Berne, Switzerland. The main discussion will be the "Principles and Practice in Maintaining Asepsis During Ophthalmic Operations."

Further information may be procured from the honorable secretary and treasurer, I. C. Fraser, 12 St. John's Hill, Shrewsbury, Shropshire, England.

**The Ophthalmological Society of Australia.**—At the annual meeting, held in the first week of October, the following officers were elected: president, Dr. Arthur H. Joyce; vice president, Dr. E. J. McGuinness; honorary treasurer, Dr. A. E. F. Chaffer; honorary secretary, Dr. A. L. Lance, 27 Commonwealth Street, Sydney.

there had been an anterior synechia, which was freed without incident. As the result of the development of glaucoma in this case, the author advocates trephination prior to the corneal grafting. In the second case, in which there was a strong nystagmus, the graft was successful, with some improvement in vision. These cases are of interest from two points of view: First, it is possible to carry out this procedure in young subjects, and, second, the process of growth does not interfere with the obtaining of a good result. He had come, therefore, to believe that a delay of more than three years is not indicated.

S. B. MARLOW.

CORNEAL GRAFTS IN TWO PATIENTS WITH GROENOW'S DISEASE.  
E. HARTMANN and P. V. MORAX, Bull. Soc. d'opht. de Paris,  
March-April 1947, p. 121.

Usual treatment, including the wearing of contact lenses, did not in any way change the progress in either patients with nodular disease of the cornea. Seven months after the corneal transplantation, the vision of the first patient had increased from 1/25 to 1/3. In about the same length of time a transplant gave the second patient an increase in vision of from 1/25 to 1/10. Spots in the posterior portion of the cornea were still visible with the slit lamp in each eye seven months after the operation, but there seemed to be no increase in size of these dots.

L. L. MAYER.

CORNEAL CHANGES DURING TREATMENT WITH ARSPHENAMINE.  
T. A. J. VAN DOORMAAL, Nederl. tijdschr. v. geneesk. 91:2751  
(Sept. 27) 1947.

According to van Doormaal, treatment with arspenamine preparations may cause serious corneal lesions. He describes the case of a man aged 47 in whom, during treatment with arspenamine and a bismuth compound for syphilis, there developed severe dermatitis, conjunctivitis and bilateral corneal ulcers with perforation. The patient recovered slowly from his dermatitis and became almost blind. Corneal lesions which develop during treatment with arspenamine usually, but not always, appear in the course of arspenamine dermatitis.

J. A. M. A. (W. ZENTMAYER.)

### Experimental Pathology

EFFECTS OF NITROGEN MUSTARD ON THE PERMEABILITY OF THE BLOOD-AQUEOUS HUMOUR BARRIER TO EVANS BLUE. H. DAVSON and J. P. QUILLIAM, Brit. J. Ophth. 31:717 (Dec.) 1947.

The work described was undertaken to find out whether the rate of penetration of Evans blue into the eye could be used as an index of the severity of a lesion caused by nitrogen mustard (methyl-bis-[B-chloroethyl]-amine hydrochloride), and to this end the effects of three preparations of the substance, known to have different toxicities, were compared. The results showed that this was indeed possible; moreover, an extremely interesting dependence of the severity of the lesion in one



### Bacteriology and Serology

A COMPARISON OF ANISEIKONIC TEST INSTRUMENTS AND PROLONGED INDUCTION OF ARTIFICIAL ANISEIKONIA. P. W. MILES, *Am. J. Ophth.* 31: 687 (June) 1948.

Miles states that artificially produced aniseikonia causes distortion of objects, interferes with vision and, if the size difference is more than 5 per cent, prevents fusion and stereopsis altogether. He describes experiments in which meridional magnifying lenses were worn for prolonged periods.

W. S. REESE.

### Congenital Anomalies

CRATER-LIKE HOLES IN THE OPTIC DISC. E. ROSEN, *Brit. J. Ophth.* 32: 465 (Aug.) 1948.

Rosen describes and pictures 7 cases of holes in the optic disk. Such holes may erroneously be regarded as evidence of glaucomatous changes, particularly when there are pupillary inequalities, atrophy of the iris or field defects. These holes may also be present in amblyopic eyes, in which instance recognition should lead to avoidance of occlusion therapy. The field defect may be rather constant and may be recognized by an observant patient. The possibility that such a "pit" will extend back into the orbit and unite with a cyst, thus producing unilateral exophthalmos, should also be borne in mind.

W. ZENTMAYER.

### Cornea and Sclera

STIMULATION OF CORNEAL EPITHELIZATION WITH TOPICAL APPLICATION OF ERYTHROCYTES. F. W. NEWELL, *Am. J. Ophth.* 30: 1238 (Oct.) 1947.

Newell found that treatment of experimentally abraded corneas with an ointment containing washed, packed human red blood cells resulted in significantly increased rates of epithelization in the guinea pig.

W. S. REESE.

CYANIDE INHIBITION OF CORNEAL RESPIRATION. W. A. ROBBIE, P. J. LEINFELDER and T. D. DUANE, *Am. J. Ophth.* 30: 1381 (Nov.) 1947.

Robbie, Leinfelder and Duane found that corneal respiration is almost completely inhibited by  $10^{-3}$  molar solution of hydrogen cyanide, but that recovery from exposure to cyanide is rapid.

W. S. REESE.

CORNEAL GRAFTS IN THE CHILD AND THE ADOLESCENT. G. E. JAYLE, *Arch. d'ophth.* 7: 148, 1947.

The author reports a case of corneal graft in a child aged 11 who had typical interstitial keratitis with extensive vascularization. He reports a second case of such a graft in an adolescent aged 16, who had bilateral amblyopia due to a leukoma of the cornea, resulting from ophthalmia neonatorum. The author describes his technic. In the first case glaucoma developed approximately six weeks after the operation and was controlled by trephining. About fifteen days after operation

speed of work recognition and intelligence quotients below 90 occur more frequently among poor readers than in the other groups tested, but that the median amount of defectiveness is not appreciably greater in any of the groups. This conclusion is in line with the clinical observation that poor readers are often troubled to a greater extent than others by such handicaps as low degrees of hypermetropia and other ocular defects.

W. S. REESE.

NEW CONCEPTS CONCERNING OCULAR COMPLICATIONS FOLLOWING VACCINATION. E. ROSEN, *Ophthalmologica* 115: 321 (June) 1948.

In the spring of 1947 mass vaccinations against smallpox were performed in New York city. Ocular complications were seen from six to twelve days after the vaccination. They included interstitial keratitis associated with vestibuloauditory symptoms, metaherpetic keratitis, dendritic keratitis, exudative chorioretinitis, central serous retinopathy, iritis and panophthalmitis, thrombophlebitis and lesions of the extra-ocular muscles. The lesions of the retina, such as edema, endophlebitis, perivasculitis and neuritis, are closely related to the changes in the brain found in postvaccinal encephalitis. The literature on this subject is reviewed.

H. P. KIRBER.

General Diseases

SCLERODERMA AND LESIONS IN THE FUNDUS. E. HARTMANN, P. COLLIN and P. VERGNE, *Ann. d'ocul.* 181: 220 (April) 1948.

The authors present the case of a patient with scleroderma and an unusual lesion in the fundus of each eye. The posterior poles of both eyes were seeded with bright spots of varying size, shape and color. These spots were not confined to the distribution of the retinal vessels, and they diminished in number toward the periphery. With the binocular ophthalmoscope, they appeared to be deep, and the retina did not seem to be elevated over the lesions. In the right eye the macula was involved, though corrected vision was 10/10. The macula in the left eye was clear, and vision was 7/10. The visual fields and retinal arterial pressure were normal.

Clinically the spots appeared much like drusen; but, because of the patient's youth and the abundance of the lesions, the authors do not feel that the changes were typical of drusen. They believe that the lesions were caused by a disturbance in Bruch's membrane similar to that in drusen, but that in their case the changes were related to the generalized scleroderma.

P. R. McDONALD.

ACUTE OCULAR MANIFESTATIONS OF ARIBOFLAVINOSIS. H. J. STERN, *Ophthalmologica* 114: 103 (Aug.) 1947.

If the vessels of the limbal plexus throw out new capillaries, a diagnosis of riboflavin deficiency can be made in the presence of any primary corneal lesion. A case is presented in which the diet was grossly deficient in riboflavin and recovery occurred promptly with riboflavin therapy.

F. H. ADLER.

eye on the condition of the other eye became manifest; for this reason, the part of the work bearing on this point is being published.

It is well known that the permeability of the capillary endothelium to proteins, and therefore to Evans blue, is largely determined by the physiologic state of the capillaries; if they are dilated, their permeability is high; if contracted, it is low. If the lesion produced by a high concentration of nitrogen mustard in one eye causes a reflex dilatation of the vessels in the iris of the other, then the phenomena described here are explicable on the basis of reflex action. In confirmation of this statement, it has been noted that after instillation of nitrogen mustard into the left eyes of a series of animals a ciliary injection was observed in the untreated (right) eye; only on one occasion, however, was it possible to demonstrate that injected Evans blue appeared in the contralateral eye. One may conclude, therefore, that a severe lesion in one eye potentiates the action of a mild nitrogen mustard agent in the other by reflex action; in the present case, the effects of this potentiation are greater with the milder than with the stronger solution.

W. ZENTMAYER.

### General

#### VIRUS STUDIES IN LYMPHOMATOID DISEASES OF THE OCULAR ADNEXA.

A. E. BRALEY and R. C. ALEXANDER, *Am. J. Ophth.* 30:1369 (Nov.) 1947.

Braley and Alexander present a preliminary report of a new virus. This virus was obtained from lymph nodes and the submaxillary gland of a patient with a form of rapidly progressive exophthalmos. The virus produces encephalitis in rabbits, guinea pigs and mice and grows well in tissue culture. The cellular response to the virus in animals is predominantly lymphocytic. The virus is submicroscopic. It is neutralized by blood serum from the patient. Normal human serum and the blood serum of most laboratory animals contain no neutralizing antibodies. The virus has not been identified in any known classification.

W. S. REESE.

#### READING DIFFICULTY (DYSLEXIA) FROM THE OPHTHALMIC POINT OF VIEW. G. E. PARK, *Am. J. Ophth.* 31:28 (Jan.) 1948.

Park concludes that dyslexia is an entity and is sufficiently common to require attention. Its correction requires study of the child from the physical, emotional and pedagogic points of view. He makes a somewhat detailed analysis of the ophthalmic findings that were coincidental with other symptoms in a series of 133 cases of dyslexia.

W. S. REESE.

#### COMPARISON OF EYE CONDITIONS AMONG 1,000 READING FAILURES, 500 OPHTHALMIC PATIENTS, AND 150 UNSELECTED CHILDREN. T. H. EAMES, *Am. J. Ophth.* 31:713 (June) 1948.

Eames reports his observations in a comparative study of the ocular conditions of 1,000 poor readers, 500 patients with ophthalmic disorders and 150 unselected children. His study indicates that for the present group at least hypermetropia, exophoria at the reading distance, retarded

in the left frontal, temporal and occipital bones. The sphenoid was fully involved. The orbital fissure could not be demonstrated; the frontal and maxillary sinuses were obliterated. The only other bones affected were the left side of the mandible and the lower third of the right humerus.

A corneoscleral trephining of the left eye was done. The author thinks there is little doubt that the ophthalmic condition was due to the abnormal bony formation.

W. ZENTMAYER.

### Instruments

SIZE OF LINE IN THE MADDOX-ROD TEST. R. G. SCOBEE and E. L. GREEN, *Am. J. Ophth.* 31: 697 (June) 1948.

Scobee and Green conclude that variation in measurements of heterophoria is not due to variations in the size of the line produced by different-sized muscle lights.

W. S. REESE.

SOME PROBLEMS IN THE CALIBRATION OF TONOMETERS. JONAS S. FRIEDENWALD, *Am. J. Ophth.* 31: 935 (Aug.) 1948.

Friedenwald presents a preliminary report on the calibration of tonometers. He finds that the calibration scales of Schiøtz and McLean are both too high and states the belief that the average normal intraocular pressure is between 18 and 19 mm. of mercury. He discusses ocular rigidity and estimates the coefficient of the average normal eye as 0.0245, corresponding to an increase of 5.8 per cent in the intraocular pressure for a displacement of 1 cu. mm. of fluid.

W. S. REESE.

A LOW POWER INFRA-RED MICROSCOPE. T. STUART-BLACK KELLY, *Brit. J. Ophth.* 32: 396 (July) 1948.

Kelly describes a low power infra-red microscope. The viewing device can replace the normal binocular microscope on a slit lamp table. Incorporated in the microscope is an infra-red converter tube. Considerable density of cornea can be penetrated. A contact glass improves penetration of a rough surface. Penetration of cataract seems to depend on the chemistry of the cataract.

W. ZENTMAYER.

A SIMPLE, SELF-REGISTERING PERIMETER. W. WEIDMANN, *Ophthalmologica* 115: 332 (June) 1948.

The perimeter consists essentially of a hollow sphere made of transparent plastic material, a self-registering mechanism and a projector for the test object, which appears as a spot of light on the outside and the inside of the sphere. The instrument is simple and is claimed to be inexpensive. It is manufactured in Switzerland.

H. P. KIRBER.

### Lens

INTRACAPSULAR EXTRACTION OF CATARACT. C. DUVERGER and P. BREGAT, *Arch. d'opht.* 7: 379, 1947.

The authors emphasize the advantages which a keratome incision with enlargement by scissors affords. The suture is described, and the value of a good capsule forceps and the use of the left hand in the pro-

## Glaucoma

A STATISTICAL STUDY OF GLAUCOMA. J. C. HOLST, Am. J. Ophth. 30:1267 (Oct.) 1947.

Among 12,127 admissions to the University eye clinic in Oslo, Norway, were 2,024 patients, or 8.4 per cent, with glaucoma simplex; 1,261 patients, or 62.3 per cent, were men, and 763 or 37.7 per cent, were women. The fact that men greatly outnumbered women is the more surprising, as in the age group (over 50) in which the incidence of glaucoma is the highest the percentage of men to women is 45.5:54.5.

Hypermetropia was present in 25 per cent of patients with glaucoma simplex; emmetropia, in 50 per cent, and myopia, in 19 per cent; 5 per cent were astigmatic. Inverse astigmatism was found in as great a proportion as 2 per cent. Of 459 patients examined for exfoliation of the lens capsule, the lesion was present in 375 (82 per cent).

Of 53 patients with unilateral glaucoma in whom exfoliation was found only on one side, it was always in the eye with the glaucoma. Exfoliation in the healthy eye, but not in the glaucomatous eye was never observed.

W. ZENTMAYER.

THE CLINICAL USE OF DI-ISOPROPYL FLUOROPHOSPHATE (DFP) IN CHRONIC GLAUCOMA. W. G. MARR, Am. J. Ophth. 30:1423 (Nov.) 1947.

Marr concludes that di-isopropyl fluorophosphate has little chance of success in cases in which the commonly used miotics fail and that the drug is not always innocuous.

W. S. REESE.

REOPERATION FOR GLAUCOMA. P. C. KRONFELD, Pennsylvania M. J. 51:148 (Nov.) 1947.

In about 20 per cent of unsuccessful trephine operations by gonoscopic examination the trephine opening proved to be plugged on the inside by the ciliary body, lens or iris. In about 80 per cent there was closure of the outer aperture of the trephine canal.

Not more than 20 per cent of second trephinations were successful. The most favorable site for the second operation seemed to be in the horizontal meridian. A typical sequence of surgical procedures is described, starting with an external filtering operation and followed, if necessary, by one or two cyclodialyses, which are followed, if necessary, by one of two cyclodiathermies. This sequence of operations is capable of normalizing the ocular tension in 85 per cent of chronic simple, wide angle glaucomas

W. ZENTMAYER.

GLAUCOMA SECONDARY TO FIBROCYSTIC DISEASE OF BONE. J. W. E. CORY, Brit. J. Ophth. 31:731 (Dec.) 1947.

A farmer aged 58 complained of loss of vision and discharge from the left eye. For at least forty years there was a swelling over the left temporal region.

The left eye showed slight proptosis and vision was 6/60. Intra-ocular pressure was 33.75 mm. of mercury. The optic disk was cupped. The field of vision was restricted to a small area in the upper and outer quadrant. Roentgenograms showed a honeycombed condition of bone

TREATMENT OF PHORIAS IN ADULTS. E. HEALY, *Am. J. Ophth.* 31:703 (June) 1948.

Healy concludes that phorias respond readily to treatment and that the aim should be relief of symptoms and not orthophoria.

W. S. REESE.

PROBLEMS IN RESEARCH IN ORTHOPTICS. F. E. JACKSON, *Am. J. Ophth.* 31:805 (July) 1948.

Jackson concludes that much time and preliminary effort involved in research can be minimized by (1) a definite system in keeping records of diagnosis, treatment and follow-up observations on cases, (2) an abstract file of current publications and (3) a diagnostic file of case histories. Analysis of cases represents the bulk of orthoptic research. Results of such analysis can be presented in three ways: as a statistical survey, as a comparative study and as a report of individual cases.

Five benefits are to be derived from research in orthoptics: (1) clarification of orthoptic terminology, (2) standardization for evaluation of results, (3) elimination of variable factors, (4) collection of sensory data and (5) a better sense of perspective for routine treatment.

W. S. REESE.

### Parasites

HYDATID OF THE ORBIT. H. HOLLAND, *Brit. J. Ophth.* 32:395 (July) 1948.

Holland has seen 8 cases of hydatid cyst of the orbit. The cyst is generally on the nasal side and always in the upper fornix. In the early stage there is some fulness of the upper fornix, but in the later stages proptosis is so extreme that the eye cannot be closed. Vision is usually good. The diagnosis can be confirmed by aspiration of the contents of the tumor and examination for hooklets after the patient has been prepared for operation. If hooklets are found, the needle should be left in place and the cyst excised at once.

W. ZENTMAYER.

CHRONIC SUPERFICIAL PUNCTATE KERATITIS CAUSED BY THE ONCHOCERCI VOLVULUS. M. APPELMANS, *Ophthalmologica* 114:129 (Sept.) 1947.

The case histories of 2 patients with ocular onchocercosis are reported, and the author stresses his belief that a diagnosis of onchocercosis is possible only when the presence of the mobile larvae is confirmed by biomicroscopy. It is not sufficient evidence that one obtains a history of the patient's having been in the tropics and of having had a chronic superficial punctate keratitis or a uveitis with eosinophilia demonstrated in the blood. The parasites must be found in the eye. The mere presence of the larvae of *Onchocerca volvulus* or *Onchocerca caecutiens* in the anterior chamber is not sufficient to produce iritis, but an allergic factor must also play a part in the origin of the keratitis and the uveitis. The only form of treatment known is the extirpation of the filaria nodules. This prevents the development of the embryos and hinders the entrance of the larvae into the eye as long as the carrier is guarded against new infection. The author recommends application

duction of pressure during extraction is pointed out. The method of suturing by half-knots is described; finally, the precautions necessary in regard to the iris and the incidence of loss of vitreous are indicated. The authors' procedure is described in some detail.

S. B. MARLOW.

CONNECTION BETWEEN THE POSITION OF ZONULAR OPACITIES IN THE LENS AND THE TIME OF THEIR FORMATION ESTIMATED FROM SIMULTANEOUSLY OCCURRING ENAMEL HYPOPLASIA. A. HUGGERT, *Acta ophth.* 26: 7, 1948.

There is a diversity of opinion in regard to the time of formation of the various layers of the lens that constitute the zones of optical discontinuity. The author examined a number of zonular cataracts, took measurements of their size, noted their position in the lens and correlated these observations with the probable time of onset of a coexisting enamel hypoplasia. The examinations show that the lenticular layer of the outer embryonic nucleus is established at the time of birth while the layer within the innermost part of the adult nuclear zone is probably established between the age of 1 and 2 years.

O. P. PERKINS.

### Lids

CORRECTION OF PTOSIS BY TUCKING OF THE LEVATOR. A. GARDILCIC, *Ophthalmologica* 115: 269 (May) 1948.

The advantages and disadvantages of accepted procedures for the correction of ptosis are discussed, and the literature is reviewed. Gardilcic proposes to expose the levator from the outside, then anchor three double-armed sutures in the muscle fibers and attach these to the anterior surface of the tarsal plate, thus effecting a tucking and advancement of this muscle. In cases of total ptosis, the tarsal plate is exposed extensively, and the sutures are attached to it close to the lid margin. To prevent an eversion of the upper lid, additional sutures are placed through the tucked muscle and the upper margin of the tarsal plate. The advantages claimed for this procedure are as follows: 1. The amount of correction can be varied by anchoring the sutures at various levels of the muscle and by attaching them at different levels to the tarsal plate. 2. There are no anatomic derangements, and the procedure can be repeated if necessary. 3. The technic is fairly simple.

The procedure is recommended for partial, as well as for total, ptosis.

H. P. KIRBER.

### Ocular Muscles

THE VERGENCE TEST: AN EVALUATION OF THE VARIOUS TECHNIQUES. W. H. FINK, *Am. J. Ophth.* 31: 49 (Jan.) 1948.

Fink concludes that the vergence test is an important part of the ophthalmologist's daily routine. It is generally admitted that the various technics used for this test do not give consistent results. An attempt is made to determine which is the most efficient and the most dependable. Certain changes in technic seem to increase the efficiency of the test. These changes in technic, according to the data, produce more dependable readings, cause less fatigue to the patient, make the test more understandable to the patient, save time for the examiner and give a more correct interpretation of the findings.

W. S. REESE.

if the subject possesses good visual acuity. The paper is illustrated, and it should be possible for any one to construct an instrument like the one described.

S. B. MARLOW.

A STUDY OF REFRACTION ACCORDING TO THE TECHNIC USED BY SOME NORTH AMERICAN OPHTHALMOLOGISTS. W. H. CRISP, *Bol. Hosp. oftal. Ntra. Sra. de la Luz* 3: 217 (Jan.-Feb.) 1947.

The author states that many ophthalmologists, in their enthusiasm for surgery, neglect the universal importance of refraction. Certain details of technic for the measurement of spherical errors of refraction are mentioned, but the greater part of this paper deals with astigmatism and with methods of examination which are generally not mentioned or are insufficiently described in the textbooks. The author advises the fogging method in examination of patients with hypermetropia. The technic of the use of the crossed cylinder is described in great detail.

M. E. ALVARO.

TOLERANCE OF CONTACT LENSES. S. GYORFFY and A. KAHAN, *Ophthalmologica* 116: 1 (July) 1948.

Fifteen persons were tested who complained that they were unable to wear their contact lenses for any useful length of time. Assuming that the contact lens causes irritation of the cornea and conjunctiva, decrease in oxygen metabolism and liberation of histamine, the authors applied a 2 per cent solution of antistin® (2-[N-phenyl-N-benzyl-amino-methyl] imidozotin) and privine® (naphazoline hydrochloride) five minutes prior to wearing the contact lenses. A blanching of the conjunctival vessels resulted, with decrease in corneal sensitivity and no change in the size of the pupil. Nine of the 15 patients tested were able to wear their contact lenses for considerably longer periods after the local application of this drug.

H. P. KIRBER.

### Retina and Optic Nerve

CAPILLARY FRAGILITY AND CUTANEOUS LYMPHATIC FLOW IN RELATION TO SYSTEMIC AND RETINAL VASCULAR MANIFESTATIONS: RUTIN THERAPY. J. M. DONEGAN and W. A. THOMAS, *Am. J. Ophth.* 31: 671 (June) 1948.

Donegan and Thomas found abnormally increased capillary fragility associated with arteriosclerosis and hypertension, especially in cases of diabetes associated with retinopathy. Rutin decreased the capillary fragility, but not to normal, in cases of diabetes with retinopathy but did not improve vision. It may, however, be significant that there was no loss of vision during a ten to twelve month period of treatment. Rutin appears to be of benefit in cases of Eales's disease and central serous retinopathy.

W. S. REESE.

A CASE OF A GRÖNRLAD-STRANDBERG SYNDROME, WITH DISCIFORM DEGENERATION OF THE MACULAE. G. HIBBERT, *Brit. J. Ophth.* 32: 478 (Aug.) 1948.

The patient, a man aged 38, first noticed distortion of objects to his right side. When he was first observed, there were several small ovoid



of an ointment containing 5 per cent mild mercurous chloride U. S. P. in the conjunctival sac in those cases of superficial punctate keratitis caused by filariasis in which parasitic tumors are not present.

F. H. ADLER.

### Pharmacology

OCULAR EFFECT OF SEVERAL IRRITANT DRUGS APPLIED DIRECTLY TO THE CONJUNCTIVA. J. J. ESTABLE, *Am. J. Ophth.* 31:837 (July) 1948.

Estable concludes that the irritant local effects of drugs on the ocular membranes are studied by direct instillation into the conjunctival sac of one eye of the rabbit, the other eye being treated with isotonic solution of sodium chloride as a control.

The following drugs were tested, in several concentrations: anthraquinone, arsenic trioxide, chrysarobin, colchicine, emetine, histamine, paraphenylenediamine, podophyllin, quinone, menadione and resorcinol.

The clinical manifestations produced by different concentrations of these drugs are described in detail, and a classification in order of potency and concentration is given.

The relation of solubility, physical state, concentration, time of contact and frequency of application of the drugs and their irritant effect is discussed, as are the immediate, acute and delayed inflammatory changes and the opacity of the cornea and its vascularization.

W. S. REESE.

INTRAVITREOUS STREPTOMYCIN: ITS TOXICITY AND DIFFUSION. P. A. GARDINER, I. C. MICHAELSON, R. J. W. REES and J. M. ROBSON, *Brit. J. Ophth.* 32:449 (Aug.) 1948.

The authors describe the methods employed in animal experimentation. Intravitreal injection of 2,000 micrograms of streptomycin acts as a depot from which streptomycin diffuses slowly, chemotherapeutic concentrations still being present in the ocular fluids after three days. The toxic effects of streptomycin introduced into the vitreous in doses of 1.2 and 3.0 mg. result in serious retinal damage. The authors state that these observations are at variance with those of Bellows and associates, who showed that intravitreal injection of streptomycin in amounts of 25 to 1,000 micrograms per dose failed to produce any permanent damage to the fundus. The difference between these results may well be due to differences in the toxicity of the streptomycin used, but the data suggest that at present great caution should be used in the intravitreal use of streptomycin.

W. ZENTMAYER.

### Refraction and Accommodation

A SUBJECTIVE PROCEDURE FOR MEASURING AMETROPIA WITHOUT TEST CHART OR GLASSES BY THE USE OF A VARIABLE BAYONET. P. FABRE, *Arch. d'opht.* 6:436, 1946.

After presenting some mathematical considerations, the author proceeds to describe a box which it is possible to rotate on a standard, calibrated to indicate the amount of refractive error by the observation of slits on the screen. The method is reported to be rapid and precise

visual acuity and field of vision. Measurements of the critical frequency of fusion, however, will show a definite and permanent defect which includes the whole area that was previously detached.

H. P. KIRBER.

### Tumors

INTRAEPITHELIAL EPITHELIOMA OF THE CORNEA AND CONJUNCTIVA (BOWEN'S DISEASE). B. ESTERMAN, J. LAVAL and C. OKRAIN-ETZ, *Am. J. Ophth.* 30: 1537 (Dec.) 1947.

Esterman, Laval and Okrainetz report a case of Bowen's disease in which cure was apparently effected by radiotherapy without any untoward action on the lens.

W. S. REESE.

MELANOMA OF THE PAPILLA: REPORT OF A CASE. P. SATANOWSKY and P. KURLAT, *Arch. de oftal. de Buenos Aires* 22: 141 (July-Aug.) 1947.

A patient aged 46 presented a pigmented tumor on a part of the optic papilla. The growth had not undergone any change over a period of six years of close observation. Visual acuity and the field of vision had remained normal, although for a year and a half the intraocular pressure was increased; this high pressure disappeared with medical treatment.

M. E. ALVARO.

CHONDROSARCOMA OF THE ORBIT. P. SHARKANSKAYA, *Vestnik oftal.* 25: 38, 1946.

A man aged 56 noted proptosis of the right eye a few months previously. Examination revealed a firm growth the size of a bean at the upper lateral region of the right orbit. The movement of the eye outward and upward was limited. There was exophthalmos, and fundoscopic examination showed papilledema. A malignant growth was suspected (rapid growth of the neoplasm), and an operation was performed. On orbitotomy a tumor was observed outside the muscle funnel; but it could not be removed, so that the Krönlein operation had to be employed. The tumor, the size of a pigeon egg, was excised. After the operation the eyeball collapsed. On the fourth day exophthalmos was still present, with ulceration of the cornea. Within the next two weeks the exophthalmos disappeared and the corneal ulcer healed.

The pathologist made the diagnosis of chondrosarcoma (polymorphism of the cartilage cells and a soft basic substance).

The patient refused to have exenteration of the orbit, and six courses of high voltage roentgen therapy were applied.

Chondrosarcoma is rare; its growth is rather slow, and metastases are not frequent.

O. SITCHEVSKA.

### Uvea

VOGT-KOYANAGI SYNDROME. M. PUIG SOLANES, *An. Soc. mex. de oftal. y oto-rino-laring.* 21: 12 (Jan.-March) 1947.

The first case was that of a Negro woman aged 25. At the end of two weeks of failing sight, vision in both eyes was blurred. There was a flat detachment of the greater part of both retinas. Eleven days

patches of exudate with faintly pigmented borders scattered throughout the fundus. One year later patches of exudates were present at the macula, and angioid streaks appeared. Changes in the skin appeared during the eighteen months in which the eyes were under observation, though there was a long history of unusual texture of the skin. There was increasing deterioration of vision; when last noted, vision was less than 6/60 in the right eye and 6/24, with eccentric fixation, in the left eye.

W. ZENTMAYER.

HISTOLOGICAL FINDINGS IN A CASE OF ANGIOID STREAKS. F. H. VERHOEFF, *Brit. J. Ophth.* 32: 531 (Sept.) 1948.

The eye studied histologically by Verhoeff was from a patient of the late Grady E. Clay, who reported that a few angioid streaks were present in both fundi. The only abnormal histologic changes in the fundus of this eye, aside from the two drusen at the margin of the optic disk, were the basophilia of Bruch's membrane and the gaps in this membrane. The article contains a critical survey of the literature bearing on the histologic features of this condition. The author concludes that angioid streaks result from ruptures of a basophilic Bruch's membrane. The gaps are widened by the elastic tension of the choroid. In the ophthalmoscopic picture, the basophilic condition (calcification) brightens the contiguous fundus and makes conspicuous the dark red choriocapillaris, exposed beneath the pigment epithelium by the ruptures. The streaks are later often altered in appearance by proliferative changes along or within them. The similar ruptures that occasionally occur in senile eyes do not widen into visible streaks, probably because the senile choroid loses its elasticity before Bruch's membrane becomes calcified. Other lesions in the macula and elsewhere in the fundus which are associated with angioid streaks are usually due to proliferative changes involving the pigment epithelium, such as occur under senile degenerative conditions. The subretinal hemorrhages in the macula and elsewhere may be due to ruptures of the choriocapillaris caused by fractures of the calcified membrane. When such a hemorrhage lifts up the pigment epithelium in the macula, "disciform degeneration" results. Hemorrhages arising within the retina are probably explained, as is also circinate retinitis, by the vascular changes that commonly occur in cases of angioid streaks. The association of angioid streaks in many cases with pseudoxanthoma elasticum, in some cases with osteitis deformans (Paget's disease) instead and in still other cases with neither of these conditions is difficult to explain, as is also their association with cardiovascular disease. A possible explanation is that these associations are dependent on hereditary linkages.

W. ZENTMAYER.

MODIFICATIONS IN THE CRITICAL FREQUENCY OF FUSION AFTER SURGICAL REPAIR OF DETACHMENT OF THE RETINA. R. WEEKERS and F. ROUSSEL, *Ophthalmologica* 115: 297 (May) 1948.

Operations for detachment of the retina performed within four weeks after the onset will frequently give a perfect result with respect to

## Book Reviews

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**Report of the Committee on Trachoma of the Second Pan-American Congress of Ophthalmology, Arq. brasil. oftal. 9: 66-84 (April) 1946.**

The president of the Second Pan-American Congress of Ophthalmology appointed a committee on trachoma to collect information on the incidence of trachoma in the Americas. This committee consisted of Dr. Ivo Corrêa Meyer (president), Dr. José A. Sená, Dr. Jorge Valdeavellano, Dr. Phillips Thygeson and Dr. Polk Richards (who later resigned). This pamphlet is the substance of their report.

In the United States the Indians are believed to have been infected originally by the Spanish invaders, whereas in Canada the Mennonites are considered responsible. Indeed, wherever this sect has settled—whether in Canada or in South America—trachoma has soon become endemic. It seems that they consider the disease a divine punishment, and any attempt to treat it as a flouting of God's will. In the United States, it is estimated that there are 25,000 cases of trachoma among the Indians and 33,000 among other races spread throughout the country.

In Mexico and Central America, Cuba and Haiti, trachoma is not a great problem. In fact, the disease has never been reported in Santo Domingo, Guatemala, Costa Rica, Panama, British Guiana, Jamaica, the Bahamas, Barbados, Bermuda or Trinidad.

Apparently, Brazil is the South American country most afflicted with trachoma. The problem is indeed serious, as large numbers in the states of São Paulo and Rio Grande do Sul are affected. The government is taking energetic prophylactic and curative measures.

In the Argentine, trachoma is endemic in the north, but the capital, Buenos Aires, is free of the disease. Bolivia and Chile have no great problem nor had Paraguay until the Mennonites came. The disease has now followed them into the northern part of that country. The total number of cases in Uruguay is estimated at 1,500. Reports from Peru indicate similar scanty records. Ecuador, Colombia and Venezuela did not answer their questionnaires, but from the national medical literature it appears that the problem of trachoma is not a pressing one.

The contribution ends with the announcement that trachoma is caused by a large virus. The recent therapy with sulfonamide drugs is commented on, in effect, as follows:

"In a disease of chronic evolution, with changeable clinical aspects—latent periods alternating with periods of activity—it is difficult to consider a cure as permanent. The therapeusis, as well as the diagnosis, is made difficult by the doubt concerning the etiology of the disease. One speaks of a clinical diagnosis as one speaks of a clinical cure. It is too early, therefore, to speak of cure of trachoma by the sulfonamide drugs; several more years of experience and observation may be necessary. . . . Up to now all treatments for trachoma have been disagreeable to the patient, being slow and painful. Even were the improvement transitory and the disease only in relapse, there is nevertheless value in the new medicament."

G. M. BRUCE.

later there were anterior uveitis and poliosis. She was treated with penicillin and typhoid vaccine. Three months later visual acuity was limited to counting fingers. The condition of the fundus is not stated.

The second case was that of a Negro woman aged 28. Four months before examination, both eyes had become blind within one week. There were precipitates on Descemet's membrane, with posterior synechias. No view of the fundus was obtained. Alopecia developed in the fourth week. The tension increased in both eyes, necessitating scleral diathermy in the left eye. Both eyes were blind.

M. E. ALVARO.

made some necessary revisions. A perusal of the table of contents will show how important these new chapters are. The forty-eight subjects are grouped in five sections: physiology, diagnostic procedures, pathology, treatment and social aspects.

The headings of a few of the chapters indicate the broad scope of the book: "Illumination," W. R. Stevens; "The Electrophysiology of the Retina," Ragnar Granit; "Senescence of the Eye," F. P. Fischer; "Gonioscopy," Manuel Uribe Troncoso; "Ophthalmodynamometry and Some of Its Clinical Applications," C. Espildora-Luque; "The Nature of Sporadic Congenital Malformations," Ida Mann; "Ocular Manifestations of Vitamin Deficiencies," G. B. Bietti; "Focal Infections," Alan C. Woods; "Virus Affections of the Eye," Arnold Sorsby; "Some Newly Defined Clinical Entities Affecting the Conjunctiva," Phillips Thygeson; "Affections of the Retinal Veins," A. J. Ballantyne; "Lesions of the Retina and Optic Nerve in Association with Blood Dyscrasias," Henry P. Wagener; "Radiotherapy in Ophthalmology," H. B. Stallard; "Sulphonamide Therapy," Arnold Sorsby; "Penicillin," Arnold Sorsby; "Some Problems of Industrial Ophthalmology," Dorothy Adams Campbell, and "Some Ocular Aspects of Aviation," P. C. Livingston.

The 169 illustrations and 3 color plates are excellent, and the guiding bibliographies add to the usefulness of the volume.

The purpose of the book is a happy one and cannot fail to be of great value and interest to all ophthalmologists.

ARNOLD KNAPP.

**Cybernetics, or Control and Communication in the Animal and the Machine.** By Norbert Wiener. Price, \$3. Pp. 189. New York: John Wiley & Sons, Inc., 1948.

This is an extremely thought-provoking book, by the professor of mathematics of the Massachusetts Institute of Technology. The subject matter ranges from mathematical calculators to the nerves and brain of the human body. It is the outcome of a monthly series of discussion meetings, the participants of which were mostly young scientists at the Harvard Medical School who gathered for dinner about a round table in Vanderbilt Hall. At each meeting, one of the group or an invited guest would read a paper on some scientific topic, generally one in which methods of methodology were the first consideration. General discussion followed, and the meetings were apparently not for those who were unable to stand frank criticism. The author, whose field is mathematics, was therefore exposed to experts in many different fields of biology and medicine. He soon became aware that there were common grounds and that the problems of one science might be solved, or at least simplified, by the solutions found in others. This book is an attempt to explain the physiology of parts of the nervous system on the engineering principles and mathematics employed in the development of calculating machines or automatic pilots, or the general principle of what are called "feed backs."

While most of the book is undoubtedly far beyond the ken of most mortals, the chapters "Computing Machines and the Nervous System," "Gestalt and Universals" and "Cybernetics and Psychopathology" are extremely interesting; and where the author descends to what he admits is probably an oversimplification of the picture, one gets a pretty good

**Le fond d'oeil des hypertendus et des cyanoses.** By Daniel Routier. Price, 1,350 fr. Pp. 100, with 232 plates. Paris: Masson et Cie.

The author, who is a cardiologist, has systematically been making an examination of the fundus in all his patients and has taken many photographs of the fundus in black and white with the Nordenson camera. He has collected 232 plates for this study of hypertension and cyanosis. As pictures of the fundus usually show the advanced or rather the terminal, stage the author has studied particularly the preceding conditions, which are more difficult to recognize, and attempts to show how the smallest vessels are affected in hypertensive conditions. The photographs have not been retouched, and each photograph is accompanied with a concise and exact commentary on the general and fundus conditions. The photographs on the whole are successful, although in some the absence of color is noticeable. An accompanying text discusses the changes in turn and, with the illustrations, explains each condition from a physiopathologic standpoint.

After a description of the normal fundus and certain changes which are not pathologic, such as opaque nerve fibers, astigmatism and myopic conus, the author proceeds to a consideration of the eyeground in hypertension. The anomalies in hypertension are grouped as follows: (1) vascular changes: tortuosities, increased reflex streak, venous compression, variation in caliber; localized spasm or generalized contracted arteries; (2) papilloretinal changes: retinal edema, juxtapapillary, perivascular; papillary edema, hemorrhages, exudates.

In one sixth of the cases no change in the fundus was present. While the author subscribes to the great value that ophthalmoscopy occupies in cases of hypertension, he places it between roentgenography and electrocardiography in order of importance as a method of examination.

In the chapter on "Interpretations of Symptoms," the author speaks of how complex are the factors which, on the one hand, cause the anatomic and functional changes in the vessels and, on the other, are followed by all the retinal lesions with which these changes are allied: edema, hemorrhages and exudates. He concludes with the statement that the ocular findings in hypertension are of prognostic value: If they are single, they signify the organic involvement of the arterial system; if multiple and advanced, they announce the serious stage of a fatal outcome. In a concluding chapter he discusses cyanosis.

Dr. Routier is to be congratulated on the publication of this excellent atlas dealing with an important branch of medical ophthalmology. He has taken advantage of modern fundus photography to illustrate his admirable description of the retinal changes observed in hypertension. The atlas shows how valuable is the information obtained by an ophthalmoscopic examination, and the book should be of great interest to the internist, as well as to the ophthalmologist.

ARNOLD KNAPP.

**Modern Trends in Ophthalmology. Volume 2.** Edited by Arnold Sorsby, M.D. Price, \$12.50. Pp. 600, with 169 illustrations and 3 color plates. London: Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 1947.

Dr. Arnold Sorsby, the editor of volume 2 of this important series, has corrected certain gaps which were discovered in the contents of volume 1 (reviewed in the ARCHIVES 24:426 [Aug.] 1940) and has

anomalies of the anterior segment of the eye and chapter 6 with traumatic lesions of the angle. Tumors of the angle are considered in chapter 7, and the author devotes chapter 8 to a consideration of anterior synechias, which he terms *goniosynechies*. Following this is a chapter on the information derived from gonioscopy in cases of iridocyclitis and uveitis. Chapter 10 deals with gonioscopy of primary simple glaucoma, chapter 11 with secondary glaucoma and chapter 12 with the gonioscopic appearance of the angle postoperatively.

Although in French, the author's style is easy, and the book is excellently documented with illustrations. It is a worthy minor companion to Troncoso's authoritative book. FRANCIS HEED ADLER.

**Handbook of Ophthalmology.** By Everett L. Goar, Professor of Ophthalmology, Baylor University College of Medicine, Houston, Texas. Price, \$5.50. Pp. 166, with 48 illustrations in text and 7 color plates. St. Louis: C. V. Mosby Co., 1948.

Goar believes that the ophthalmologic books available to the junior medical student, who ordinarily has about a dozen other subjects to occupy his attention, are too complete. The same opinion has long been held by O'Brien (O'Brien, C. S.: *Ophthalmologic Notes for Students*, Iowa City, Athens Press, 1930, p. 370) and others. Dr. Goar's lectures on ophthalmology have been illustrated and slightly expanded into this volume, which is frankly designed for the use of medical students.

The subject matter follows the conventional lines of similar textbooks and is covered in chapters on anatomy, physiology, embryology, methods of examination, refraction and diseases of the various structures, in anatomic order.

If one accepts Dr. Goar's thesis (and it certainly has merit) that such books as May's and Gifford's contain too much material, this volume should prove of great time-saving value to the medical student and should enable him to pass his examinations. He will not, of course, be exposed to as much ophthalmology as if he were to study the older texts, but he always has them available if he wishes to pursue the subject further. Dr. Goar has modestly suggested that the book is intended for students only, but it should prove a valuable guide to any teacher faced with the task of organizing, or reorganizing, a course in ophthalmology. It speaks well for the teaching of this specialty at Baylor University.

G. M. BRUCE.

**The Anatomy of the Eye and Orbit.** Third Edition. By Eugene Wolff. M.B., B.S., F.R.C.S. Price, \$12. Pp. 440, with 323 illustrations, 24 in color. Philadelphia: The Blakiston Company, 1948.

More than eighty illustrations have been added to the third, and revised, edition of this popular anatomy. The majority of the illustrations were prepared from sections made in the pathologic laboratory of what is now the Westminster branch of the combined Royal and Westminster hospitals. The main changes in the text are in the description of the ciliary muscle, the substantia propria of the cornea, the vitreous, the zonule of Zinn, the distribution of the lacrimal fluid, the mucocutaneous junction of the lid margin, the precorneal film, the retinal capillaries and the central connections of the visual apparatus.



idea of how a visual organ may function. While the book has no practical value for the ophthalmologist, it is well worth while for those who like to explore the upper ether.

FRANCIS H. ADLER, M.D.

**Diseases of the Fundus Oculi with Atlas.** By Adalbert Fuchs, M.D., E. O. Professor of Ophthalmology of the University of Vienna. First English Edition. Translated by Eric Pressburger, M.D.; Edited by Abraham Schlossman, M.D. Philadelphia: The Blakiston Company, 1949. Edition limited to 995 numbered copies.

This beautifully illustrated text on diseases of the ocular fundus is the first English edition of the author's well known book in German. It is greatly to the credit of the American publishers that they have undertaken this edition, which is limited to slightly less than 1,000 copies. The text has exceptional value because of the author's long experience in the histopathology of the eye. As a result of this, he is able to correlate the ophthalmoscopically visible changes with the histologic picture, and a unique feature of the book is the publication of plates illustrating the histopathology along with the fundus picture.

The translation by Dr. Eric Pressburger is excellent and, unlike so many translations, particularly those from the German, is in good English style with short, readable sentences. Some of this credit must also go to the editor, Dr. Abraham Schlossman.

The book is divided into the usual sections on the appearance of the normal fundus, congenital anomalies and, then, diseases of the various anatomic parts of the eye, such as the optic nerve, retina and choroid. Special chapters on certain diseases of the eye, such as glaucoma, tuberculosis, syphilis, tumors and detachment of the retina, follow.

While the plates are not as good as those in the early German and English atlases, they are the best which have appeared in recent years in any language, particularly in English. In spite of its cost, this book should be bought by all who have a serious interest in the ophthalmoscopic changes in local and general diseases.

FRANCIS H. ADLER.

**Gonioscopy.** By Dr. Jules François. Price not stated. Pp. 233, with 156 figures, 48 in color. Louvain, Belgium: Librairie R. Fonteyn, 1948.

This book was commissioned by the Belgian Ophthalmological Society and is an excellent review of what is known of the filtration angle in the normal human subject and in the various forms of glaucoma. It is written in French, but contains an excellent bibliography of the world's literature. It is of interest to note that the majority of these references are to authors in this country.

The first chapter deals with the anatomy of the normal angle. In the next chapter, the importance of the canal of Schlemm is considered, and various theories on the outflow of aqueous are enumerated. There is a good section on the aqueous veins. Noticeable for its absence is any reference to the work of Friedenwald, who, it will be remembered, was the first investigator to find efferent arteries to the canal of Schlemm. Chapter 3 deals with the technic of gonioscopy and chapter 4 with the normal aspects of the angle. Chapter 5 is concerned with congenital

## BLOOD GROUPS AND EFFECTS OF ROENTGEN IRRADIATION IN RETROLENTAL FIBROPLASIA

THOMAS O. PAUL, M.D.

BIRMINGHAM, ALA.

**R**ETROLENTAL fibroplasia is a condition usually occurring bilaterally in premature infants and unilaterally in full term infants. It is characterized by a gray pupillary reflex; retroental vascular membrane; microphthalmos; shallow anterior chamber, with anterior synechias, a feature which predisposes the eye to the development of secondary glaucoma; remains of an anterior pupillary membrane; spheroidal lens, and searching nystagmus. All the babies in the present series have deep-sunken eyes and a discoloration of the lids, such as is noted in adults after prolonged exertion without proper rest.

I shall report 12 cases of retroental fibroplasia. I have studied the blood groups in 6 of these 12 cases, including those of the mothers and fathers and determined the Rh factor for each baby. Several infants were given roentgen radiation, the total dose ranging from 400 to 1,000 r, in an attempt to devascularize the membrane.

The first reference to this condition that I could find was made by Howard,<sup>1</sup> in 1852. Since then the various clinical and pathologic aspects of the lesions have been described under various synonyms, among which are the following: persistent thickened hyaloid artery with secondary changes (Nettleship,<sup>2</sup> 1873), persistent hyaloid canal and artery (Gardiner,<sup>3</sup> 1880), persistence and thickening of the posterior fibrovascular sheath of the lens (Collins,<sup>4</sup> 1892; Pollock,<sup>5</sup> 1923), atypical development of the anterior part of the vitreous with or without per-

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From the Department of Surgery, Section of Ophthalmology, Strong Memorial Hospital of the University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

1. Howard, H.: Further Proof of the Vascularity of the Lens and Its Capsule, *Brit.-Am. J. Med. & Phys. Sc.* **7**:150-153, 1852.

2. Nettleship, E.: Vascular Cord Traversing Vitreous and Coexisting with Great Plastic Inflammation of Hyaloid, *Ophth. Hosp. Rep.* **7**:632-637, 1873.

3. Gardiner, E. J.: A Case of Persistent Hyaloid Canal and Artery, *Arch. Ophth.* **9**:473-474, 1880.

4. Collins, E. T.: Pseudoglioma, *Ophth. Hosp. Rep.* **13**:361-394, 1892.

5. Pollock, W. B. I.: Case of Pseudoglioma Due to Persistent Thickening of the Posterior Fibrovascular Sheath of the Lens, *Tr. Ophth. Soc. U. Kingdom* **43**:263-272, 1923.

The illustrations number 323, including 24 in color; these, in their clearness and selections, constitute a most important part, which with the excellence of the text, make this an important and essential book for study and reference. Though the book has been previously reviewed (*ARCH. OPHTH.* 25: 526 [March] 1941), it may not be amiss again to draw attention to a few headings in the contents: "The Visual Pathway," "The Involuntary Nervous System," "The Path of the Light Reflex," "The Development of the Eye" and "Comparative Anatomy."

The completeness, the clearness of the text, with its many practical clinical comments, and the excellence of the illustrations make this a thoroughly practical textbook, which deserves continuity of its popularity.

ARNOLD KNAPP.

**Year Book of Eye, Ear, Nose and Throat.** Edited by Louis Bothman, M.D. and Samuel J. Crowe, M.D. Price, \$4.75. Pp. 511. Chicago: The Year Book Publishers, Inc., 1948.

This year's Year Book brings again in a compact and handy form an accurate review of the past year's publications in ophthalmology. The subject of the special article written by the ophthalmologic editor, Dr. Louis Bothman, is: "When Should Cataracts Be Operated On?" The abstracts, as usual, are classified on an anatomic basis, and there are several special chapters. The one on glaucoma includes a long review of Dr. Magitot's article on the "Intracranial Origin of Glaucomatous Optic Atrophy"; in the chapter on neurology and visual fields there is a review of Dr. M. Amsler's article on "Qualitative Examination of Macular Function"; the chapter on therapy is particularly complete and even reviews an article by M. Toulant on "Tissue Therapy in Ophthalmology"; the chapter on surgery, which comprises 43 pages of the 233 pages devoted to the eye in this Year Book, illustrates the interest that the surgical part of ophthalmic practice now possesses. An index of subject matter and authors' names conclude the volume. The abstract titles are complete and the abstracting is excellently done, while the author's frequent comments are valuable.

This is a useful compendium, which can be confidently recommended to every practicing ophthalmologist.

ARNOLD KNAPP.

**Some Aspects of Oculo-Refractive Technique.** By Malcolm Cholerton. Price 21s. Pp. 144, with 23 illustrations. London, England: Hammond, Hammond, Hammond, Hammond & Company, Ltd., 1948.

In the preface, the author states that this book is "an outline of the field study which engages the ophthalmic optician." The style in which it is written assumes a fair knowledge of the subject. The style is reminiscent of Chavasse and will not be easy reading for the novice.

Although the book purports to be a compendium covering the whole field of refraction and ocular muscle imbalances in 144 pages, the author spends much valuable space on subjects of little practical importance, such as aniseikonia and dynamic retinoscopy. It is hard to see how it can be of any value to an ophthalmologist.

FRANCIS H. ADLER.

During 1946 and 1947 the premature babies born in the Strong Memorial Hospital were studied, with the collaboration of the pediatric service. There were 314 premature infants—44 were stillborn and 47 died within the first forty-eight hours after birth, leaving a total of 223 for study. All these babies weighed less than 2,500 Gm. This diagnosis of retrolental fibroplasia was made for 12 babies, 2 of whom were from other hospitals, an incidence of 4.43 per cent in premature babies of less than 2,500 Gm. When the babies who weighed less than 1,500 Gm. were included, there were 77 with the condition. Of these, 34 were stillborn, and 20 died during the first forty-eight hours of life and the eyes were not examined. Of the 23 babies in the study who weighed less than 1,500 Gm., 7, or 30.4 per cent, had the defect. Thus, the more premature the infant, the more likely is retrolental fibroplasia to be present.

Before the discussion of the cases, I shall review the embryology of this portion of the eye, as reported by Reese and Payne.<sup>17</sup> Ida Mann<sup>14</sup> and Haden.<sup>18</sup>

#### EMBRYOLOGY

*First Period* (up to 13 mm. stage).—At the 4.5 mm. stage, mesoderm begins to appear in the space between the lens plate and the optic vesicle. The mesoderm is part of the vasoformative cells which will grow in through the fetal fissure to form the hyaloid arterial system.

At the 10 mm. stage, large quantities of vascular mesoderm have grown in between the lens vesicle and the inner layer of the optic vesicle, forming the hyaloid artery, which is entering the eye through the fetal fissure.

At the 12 mm. stage the vitreous is a mass of fibrils derived from the lens and retina (ectoderm) and joining secondarily with fibrils (mesodermal) from the cells of the wall of the hyaloid artery.

At the 13 mm. stage the hyaline capsule surrounding the lens has been completely formed. The lens, therefore, no longer contributes to the formation of vitreous. Vitreous fibrils, remaining adherent to the lens capsule, condense to form a thin, fibrous envelope surrounding the lens and containing in its meshes the vessels of the vascular capsule. This fibrous capsule is the capsula perilenticularis fibrosa and originates from the lental part of the primary vitreous.

*Development of Vessels in First Period:* At the 6 to 7 mm. stage the terminal part of the hyaloid artery ends near the posterior surface of the lens plate; it sends capillary branches into the meshes of the capsula perilenticularis fibrosa, forming a vascular net over the posterior surface of the lens. This is the beginning of the tunica vasculosa lentis

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18. Haden, H. C.: Concerning Certain Phases of the Development of the Vitreous, Tr. Am. Ophth. Soc. **39**:41-48, 1941.

sistence of the hyaloid artery (Collins,<sup>4</sup> 1892), congenital membrane behind the lens (Parsons,<sup>6</sup> 1902), persistence of remains of the tunica vasculosa lentis (Brückner,<sup>7</sup> 1907), persistent posterior fibrovascular sheath of the lens (Lane,<sup>8</sup> 1919), persistence of the embryonic fibrovascular sheath of the crystalline lens (Lent and Lyon,<sup>9</sup> 1922) remains of the tunica vasculosa lentis (Gifford,<sup>10</sup> 1923), pseudo phakia fibrosa of Czermak (Lloyd,<sup>11</sup> 1931), opaque membrane behind the lens (Fuchs,<sup>12</sup> 1923), shrunken fibrous tissue cataract (Collins and Mayou,<sup>13</sup> 1925), posterior lenticonus (Collins and Mayou,<sup>13</sup> 1925), congenital connective tissue formation in the vitreous chamber (Collins and Mayou,<sup>13</sup> 1925), posterior polar cataract (Collins and Mayou,<sup>13</sup> 1925), persistent vascular sheath of the lens (Mann,<sup>14</sup> 1937), fibroblastic overgrowth of persistent tunica vasculosa lentis (Duke-Elder<sup>15</sup>), retrolental fibroplasia (Terry,<sup>16</sup> 1942, 1943 and 1945), persistent primary vitreous (Reese and Payne,<sup>17</sup> 1946).

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6. Parsons, J. H.: Microscopical Section of Pseudoglioma Due to Congenital Membrane Behind the Lens, *Tr. Ophth. Soc. U. Kingdom* **22**:253-354, 1902.

7. Brückner, A.: Ueber Persistenz von Resten der Tunica vasculosa lentis, *Arch f. Augenh.* **56**:5-149, 1907.

8. Lane, F.: Persistent Posterior Fibrovascular Sheath of Lens, *Arch. Ophth.* **48**:572, 1919.

9. Lent, E. J., and Lyon, M. B.: Persistence of Embryonic Fibrovascular Sheath of Crystalline Lens, *Am J. Ophth.* **5**:706-711, 1922.

10. Gifford, S. R.: Pseudoglioma and Remains of Tunica Vasculosa Lentis, *Am. J. Ophth.* **6**:565-571, 1923.

11. Lloyd, R. I.: Pseudoglioma, with Especial Reference to Type Associated with Remains of Tunica Vasculosa Lentis, *Am. J. Ophth.* **14**:27-33, 1931.

12. Fuchs, E.: *Text-Book of Ophthalmology*, ed. 7, Philadelphia, J. B. Lippincott Company, 1923, p. 650.

13. Collins, E. T., and Mayou, M. S.: *Pathology and Bacteriology of Eye*, ed. 2, Philadelphia, The Blakiston Company, 1925, p. 45.

14. Mann, I.: *Developmental Abnormalities of the Eye*, New York, The Macmillan Company, 1937, p. 350.

15. Duke-Elder, W. S.: *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1381.

16. Terry, T. L.: Fibroblastic Overgrowth of Persistent Vasculosa Lentis in Infants Born Prematurely: Studies in Development and Regression of Hyaloid Artery and Tunica Vasculosa Lentis, *Am. J. Ophth.* **25**:1409-1423, 1942; Extreme Prematurity and Fibroblastic Overgrowth of Persistent Vascular Sheath Behind Each Crystalline Lens: Preliminary Report, *ibid.* **25**:203-204 and 262-284, 1942; Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lens in Premature Infants: Etiologic Factors, *Arch Ophth.* **29**:54-68 (Jan.) 1943; Retrolental Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis, *ibid.* **33**:203-208 (March) 1945.

17. Reese, A. B., and Payne, F.: Persistence and Hyperplasia of Primary Vitreous (Tunica Vasculosa Lentis or Retrolental Fiberplasia), *Am. J. Ophth.* **29**:1-24, 1946.

porally. In April 1947, treatment with 100 r to the right eye was given at monthly intervals. In September 1947, the membrane was observed to be definitely thinner in the right eye. The lens was clear. No blood vessels could be seen. Vision was still limited to light perception only.

CASE 2.—B. Y. was the sixth baby; her brother and sisters had normal eyes. Her weight at birth was 1,300 Gm. The mother had had no complications or illness during pregnancy. The diagnosis was made by a pediatrician in September 1946, when the baby was 3 months old. Ophthalmologic examination, with the infant under anesthesia, showed in each eye a shallow anterior chamber, anterior pupillary membrane, irregular pupil and a definite vascular membrane on the posterior surface of the lens. Tonometric readings (Schiøtz) showed 18 mm. in the right eye and 20 mm. in the left eye. Roentgen radiation, 100 r, was delivered to each eye on April 21, June 16 and July 14, 1947 (factors: 85 kilovolts, 10 milliamperes, nine and one-half seconds' exposure, 10 cm. distance, 4 mm. portal, 1 mm. aluminum filter). The baby's blood was found to be Rh negative, type O M; the mother's, Rh positive, type O M, and the father's, Rh negative, type O M N. In September 1947, the retrolental membrane still exhibited vascularity, and the lens showed no cloudiness.

CASE 3.—M. R.'s mother had had two normal children before the patient's birth. However, she had had a spontaneous abortion before and one after the birth of this baby. The child was seen when she was about 2 years of age. Her ocular condition had been diagnosed as cataract. Her weight at birth was 1,150 Gm. On Oct. 7, 1946, examination, with the child under anesthesia, showed very shallow anterior chambers; the pupils dilated to 5.5 mm. with 1 per cent atropine sulfate; tension (Schiøtz) was 50 mm. in each eye. A thick vascular membrane was observed posterior to the lens of each eye. Roentgen irradiation was started in October 1946, and 100 r was given to each eye at monthly intervals for three months. The patient's blood was Rh positive, type O M N; the mother's, Rh negative, A M type, and the father's, Rh positive O M N type. Examination in September 1947 revealed no improvement.

CASE 4.—K. M., a first baby, weighed 1,300 Gm. at birth. The mother had observed that the infant had poor vision when he was 3 months of age. Examination in April 1947, with the child under anesthesia, showed a bilateral shallow anterior chamber, anterior pupillary membrane and dense vascular retrolental membrane, and the intraocular pressure was 26 mm. (Schiøtz) in each eye. The patient's blood was Rh positive, type B M N; the mother's, Rh negative, type A<sub>2</sub>B M N, and the father's, Rh positive, type A. Beginning in May 1947, roentgen radiation was given at monthly intervals, 100 r being delivered to each eye. In September 1947 examination showed no improvement.

CASE 5.—R. B. was one of twins, whose weight at birth was 1,575 Gm. The mother had had a threatened abortion during the second month of pregnancy, after an automobile accident. Examination, with the baby under anesthesia, showed a very shallow anterior chamber bilaterally; the retrolental membrane was denser temporally and clearer nasally in each eye. The hyaloid artery and vein could be observed between the membrane and the optic disk. The intraocular pressure was 30 mm. in the right eye and 35 mm. in the left eye (Schiøtz). The patient's blood was Rh positive, type A<sub>1</sub>M N; the mother's, Rh positive, type O M N, and the father's, Rh positive, type A<sub>1</sub>M N. The diagnosis was made when the child was 18 months of age, and no therapy was given.

and is seen in the 8 to 9 mm. stage. At the 10 mm. stage these vessels have extended anteriorly to form the lateral, or capsulopupillary, portion of the tunica vasculosa lentis.

The vitreous as it now exists is known as the primary vitreous. It consists of ectoderm derived from the lens and retina, as well as mesodermal vasoformative tissue, which has formed the hyaloid artery and the posterior and lateral portions of the tunica vasculosa lentis. The formation of the hyaloid capsule at the 13 mm. stage marks the end of the period of development of the primary vitreous.

*Second Period* (12 to 65 mm. stage).—At the 16 mm. stage arterial branches arising from the hyaloid artery have begun to project into the freshly forming vitreous and are termed the vasa hyaloidea propria.

At the 25 mm. stage the anterior, or pupillary, portion of the tunica vasculosa lentis has formed.

Up to the 40 mm. stage the vitreous is still full of vessels as far as the periphery, that is, to the internal limiting membrane. After this, the smaller vessels begin to atrophy, the portion nearest to the lens remaining visible the longest, with the result that the region nearest the retina becomes free of vessels. This avascular portion is known as secondary vitreous. Its appearance is due to atrophy of the blood vessels and further formation of additional vitreous from the retina as the eye enlarges.

There occur a cessation of growth of the primary vitreous and a continued increase in the amount of secondary vitreous, which fills the eye as it enlarges, thus giving a relative decrease in size of primary vitreous.

During the eighth month, the main trunk of the hyaloid artery becomes impervious in its central part, and atrophy proceeds more rapidly in its proximal portion, so that it loses connection with the disk and floats free in Cloquet's canal from the posterior surface of the lens, atrophying during the first few years of life.

#### REPORT OF CASES

CASE 1.—S. M. was first seen when she was 3 months old. Her mother had observed that the baby did not follow moving objects as had her five siblings at the age of 2 weeks. S. M. weighed 1,550 Gm. at birth. There had been no illnesses or complications during pregnancy. The baby's blood was Rh negative, type O M, while her mother's blood was Rh positive, type O M. The father's blood was Rh negative, type O M. All had negative Wassermann reactions. The diagnosis was made on March 14, 1946, with the characteristic findings, and roentgen therapy was ordered for the right eye, the left eye acting as a control. A dose of 200 r was given at monthly intervals, with 85 kilovolts, nine seconds' exposure and a 1 mm. aluminum filter. In September 1946, six months after the beginning of therapy, the right eye showed some clearing of the membrane tem-

CASE 10.—P. M. was one of double ovum twins; the weight at birth was 1,400 Gm. The child was the product of the mother's fifth pregnancy. The other children had normal eyes. Examination, with ether anesthesia, revealed a typical picture. The family moved to California, and blood studies were not made.

CASE 11.—B. M., a twin of the baby in case 10, weighed 1,200 Gm. at birth. The findings were similar to those in case 10.

CASE 12.—Studies in this case have not been completed.

*Comment.*—Of 9 eyes treated with roentgen radiation, 3 showed slight improvement, with slight thinning of the membrane at the less dense borders of the membrane, and 6 showed no apparent change. In no case was the thinning sufficient to be regarded as of any real help preliminary to needling of the lenses. Little or no effect on the membrane vessels could be observed.

#### DIFFERENTIAL DIAGNOSIS

The following conditions must be considered in differential diagnosis:

1. Retinoblastoma. This intraocular tumor is most commonly observed in children less than 6 years of age. It is usually unilateral at first, but may be found bilaterally. Ophthalmoscopic examination shows a yellowish mass, usually in the posterior half of the globe and definitely separated from the lens. On transillumination the tumor appears dark, indicating that light does not pass through it readily. The eye is normal in size or slightly enlarged. If the baby is seen after the tumor has progressed, the eye appears enlarged and congested with purulent material in the anterior chamber, which may lead to the mistaken diagnosis of panophthalmitis. One should always suspect the presence of retinoblastoma unless a definite history of penetrating injury is given.

2. Serous detachment of the retina. The eye is usually smaller than normal or of normal size. Ophthalmoscopic examination shows a grayish mass, slightly tinged with yellow, situated away from the lens. The readiness with which it may be transilluminated shows that only fluid is behind the retina.

3. Congenital cataract. The lens is opaque in varying degrees, and the anterior chamber is normal.

4. Retrolental fibroplasia. The lens is clear, but a dense membrane is observed just behind the lens. Blood vessels are always seen on this membrane if observed carefully. The anterior chamber is shallow, and the iris appears close to the cornea. The pupil may or may not be irregular in outline, according to whether or not adhesions have formed. Small strands and remnants of pupillary membrane, like a spider web, can be observed passing across the pupil.



CASE 6.—K. M., a first baby, weighed 1,550 Gm. at birth. The diagnosis was made at 6 months of age. On Feb. 1, 1947, examination, with the patient under anesthesia, showed a shallow anterior chamber and posterior synechias, an intraocular pressure of 20 mm. (Schiøtz) and a dense, vascular retrolental membrane in each eye. The patient's blood was Rh positive, type O, while the mother's was Rh positive, type A, and the father's, Rh positive, type O. No treatment was given.

CASE 7.—J. E., a first baby, weighed 1,000 Gm. at birth. The condition was diagnosed when the infant was 3 months of age. Examination, with the child under anesthesia, showed intraocular pressure of 40 mm. (Schiøtz) in each eye, shallow anterior chambers and a small retrolental membrane temporally, with a falciform fold of retina in each eye. There was a coloboma of the optic nerve in the left eye. The patient's blood was Rh positive, type B M N.

*Data on 6 Infants with Retrolental Fibroplasia*

Case	Blood Type	Rh Factor	Wassermann Reaction	Total Dose of Roentgen Radiation
1 Patient S. M.....	OM	—	—	1,400 r
Mother.....	OM	+	—	
Father.....	OM	—	—	
2 Patient B. Y.....	OM	—	—	300 r
Mother.....	OM	+	—	
Father.....	OMN	—	—	
3 Patient M. R.....	OMN	+	—	300 r
Mother.....	AM	—	—	
Father.....	OMN	+	—	
4 Patient K. M.....	BMN	+	—	500 r
Mother.....	A <sub>2</sub> BMN	—	—	
Father.....	A	+	—	
5 Patient R. B.....	A <sub>1</sub> MN	+	—	None
Mother.....	OMN	+	—	
Father.....	A <sub>1</sub> MN	+	—	
6 Patient K. M.....	O	+	—	None
Mother.....	A	+	—	
Father.....	O	+	—	

CASE 8.—D. A., a third child, weighed 1,310 Gm. at birth. The other children had normal eyes. The mother was epileptic and had had influenza two weeks prior to delivery. The infant's condition was diagnosed at the age of 6 months. Examination, with the patient under ether anesthesia, showed small eyes, with shallow anterior chamber, persistent anterior pupillary membrane and dense, vascular retrolental membrane; the intraocular pressure was 40 mm. (Schiøtz) in each eye. One drop of 1 per cent pilocarpine nitrate was given twice a day. Roentgen radiation, in a dose of 100 r at monthly intervals, was given for four months. Six months after treatment was started there was some nasal clearing of the membranes. Vision remained limited to light perception only. Studies of the blood were not completed.

CASE 9.—F. R., a first baby, weighed 1,620 Gm. at birth. The child's condition was diagnosed at the age of 5 months. There was no toxemia or complications of pregnancy. Examination, with the patient under anesthesia, revealed a typical picture. The intraocular pressure was 12 mm. (Schiøtz) in each eye. Blood studies were not completed.

# DIFFERENTIAL DIAGNOSIS OF BOECK'S SARCOIDOSIS

Report of Ten Cases with Ocular Involvement

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AT PRESENT, the diagnosis of Boeck's sarcoidosis should be regarded as presumptive, for it is based on incomplete knowledge. There are no sure criteria for absolute diagnosis, whether from histologic sections of any tissue of the body, from laboratory tests, from roentgenograms or from complete postmortem examination. Therefore, all clinical evidence for Boeck's sarcoidosis must be most carefully evaluated before a diagnosis of the disease can be justified. The purpose of this article is to discuss the difficulties in establishing a clinical diagnosis of Boeck's sarcoidosis, to evaluate the more frequent clinical symptoms and signs and to present 10 cases of sarcoidosis and an analysis of the ocular part of the disease.

Considerable confusion exists in the differentiation of sarcoidosis from tuberculosis, silicosis, Hodgkin's disease and similar diseases. In the literature, the diagnosis of sarcoidosis is made in some cases on only scanty evidence. Rossell,<sup>1</sup> for example, made the diagnosis of sarcoidosis of the lung in 2 cases by comparing the roentgenograms of the chest with textbook pictures. King<sup>2</sup> reported 112 cases in which, in his opinion, the diagnosis of sarcoidosis was established. In 24 of these cases, he based his diagnosis on a biopsy of the skin or of a node, and in 15 cases, on the roentgenograms of the chest. These instances are mentioned not to criticize the authors, but to show the ease with which a presumptive diagnosis of sarcoidosis may be made on an insufficient basis. It has been noted that once the intriguing word "sarcoidosis" is suggested in the clinic record there is a tendency for other clinicians to accept that diagnosis without sufficient study.

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1. Rossell, G.: Deux cas de maladie de Boeck, *Rev. méd. de la Suisse Rom.* 59:420-434, 1939; cited by Ronchese.<sup>3c</sup>

2. King, D. S.: Sarcoid Disease as Revealed in the Chest Roentgenogram, *Am. J. Roentgenol.* 45:505-512, 1941.

## SUMMARY

The treatment of retrolental fibroplasia with roentgen radiation produced little change in the vascularity of the membrane. A study of the possibility that a blood factor is a cause of prematurity in this congenital malformation led to no definite conclusion. Further studies of this type at several medical centers, with possibly a central registry, might bring useful information to light.

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Schaumann<sup>5</sup> proposed that it was a difference in the type of tubercle bacillus which accounted for the difference between sarcoidosis and tuberculosis. Schaumann and Hallberg<sup>6</sup> claimed a demonstration of *Mycobacterium tuberculosis* by special staining methods and stated the belief that the peculiar structures, called Schaumann bodies, in the giant cells were, in fact, this organism. Harrell<sup>3a</sup> and Longcope<sup>7</sup> failed to find evidence of tuberculosis but expressed the belief that alterations in the chemical constituents of the blood, particularly an increase in the globulin factor, may be an aid to diagnosis.

Pinner, Weiss and Cohen<sup>8</sup> proposed that a tuberculin-neutralizing substance, anticutin, may be a factor differentiating the reactions of sarcoidosis from those of tuberculosis in the body. In subjects showing the presence of anticutin, tuberculosis may take the form of sarcoidosis. They stated that anticutins were present in 36 per cent of patients with sarcoidosis but in only 5 per cent of normal subjects and tuberculous patients.

Beinhauer and Mellon<sup>9</sup> recovered a pure culture of diphtheroid bacilli with acid-fast granules from the lymph nodes of 5 patients with sarcoidosis. These patients had negative cutaneous reactions to tuberculin, but reacted positively to a culture of diphtheroids; Schwartzchild<sup>10</sup> failed to confirm these findings. Other evidences of the relation of sarcoidosis to tuberculosis are the frequent history of tuberculous contacts in patients with sarcoidosis, the common occurrence of sarcoidosis in known tuberculous areas of the population, such as the countries of Scandinavia, and the frequency of sarcoidosis in Negro settlements, where tuberculosis is known to be prevalent. There are also not a few cases reported in the literature in which patients with a well established

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5. Schaumann, J.: On the Nature of Certain Peculiar Corpuscles Present in the Tissue of Lymphogranulomatosis Benigna, *Acta med. Scandinav.* **106**:239-253, 1941.

6. Schaumann, J., and Hallberg, V.: Koch's Bacilli Manifested in the Tissue of Lymphogranulomatosis Benigna (Schaumann) by Using Hallberg's Staining Method, *Acta med. Scandinav.* **107**:499-501, 1941.

7. (a) Longcope, W. T.: Sarcoidosis, or Besnier-Boeck-Schaumann Disease, *J. A. M. A.* **117**:1321-1327 (Oct. 18) 1941. (b) Longcope, W. T., and Pierson, J. W.: Boeck's Sarcoid (Sarcoidosis), *Bull. Johns Hopkins Hosp.* **60**:223-296, 1937.

8. Pinner, M.; Weiss, M., and Cohen, A. C.: Procutins and Anticutins, *Yale J. Biol. & Med.* **15**:459-463, 1943.

9. Beinhauer, L. G., and Mellon, R. R.: Pathogenesis of Noncaseating Epithelioid Tuberculosis of Hypoderm and Lymph Glands, *Arch. Dermat. & Syph.* **37**:451-460 (March) 1938.

10. Schwartzchild, L.: Comparison of Old Tuberculin (Koch) and Modified Tuberculin (Mellon and Beinhauer), *Arch. Dermat. & Syph.* **42**:461-465 (Sept.) 1940.

It has been stated that Boeck's sarcoidosis may affect every tissue or organ in the body.<sup>3</sup> The disease is usually described, however, as limited to certain groups of organs, such as the eye, lung, lymph nodes, skin, bones, parotid gland,<sup>4</sup> brain, thyroid, testes, nose, pharynx, sinuses, kidney, spleen, bone marrow, liver, heart and intestinal tract. In general, sarcoidosis is a relatively benign, chronic disease, occasionally punctuated by acute exacerbations. The constitutional symptoms are usually slight, and fever, while it may sometimes be present in the early stage, more frequently is entirely absent. Most writers agree that the clinical symptoms produced by sarcoidosis are usually the result of mechanical obstruction, with the consequent irritation and interference with function, rather than those of a general toxemia or systemic reaction; for example, many patients may die of failure of the right side of the heart.

#### RELATION OF SARCOIDOSIS TO TUBERCULOSIS

Boeck's sarcoidosis cannot be reasonably discussed without inclusion of some of the evidence concerned with its possible relation to tuberculosis. No concrete proof of such a relation has, as yet, been generally accepted, and the subject is controversial.

It has been claimed that tubercle bacilli have been found in some instances in stained sections of skin showing the early inflammatory lesions, but they disappear as the sarcoid nodules develop. Proponents of this theory of tuberculous origin are many, and they further propose that this early destruction of the tubercle bacilli may account for the negative reaction to the intracutaneous injection of tuberculin. Whether the early disappearance of the organism is due to its low virulence or to some special reaction of the patient is not known.

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3. (a) Harrell, G.: Generalized Sarcoidosis of Boeck, *Arch. Int. Med.* **65**: 1003-1034 (May) 1940. (b) Nickerson, D. A.: Boeck's Sarcoid: Report of Six Cases in Which Autopsies Were Made, *Arch. Path.* **24**:19-29 (July) 1937. (c) Ronchese, F.: Sarcoid and Tuberculosis: Report of a Case with Autopsy, *Arch. Dermat. & Syph.* **46**:860-871 (Dec.) 1942. (d) Reisner, D.: Boeck's Sarcoid and Systemic Sarcoidosis, *Am. Rev. Tuberc.* **49**:437-462, 1944. (e) Schaumann, J.: Lymphogranulomatosis Benigna in the Light of Prolonged Clinical Observations and Autopsy Findings, *Brit. J. Dermat.* **48**:399-446, 1936.

4. (a) Guyton, J. S., and Woods, A. G.: Etiology of Uveitis: A Clinical Study of 562 Cases, *Arch. Ophth.* **26**:983-1018 (Dec.) 1941. (b) King, M. J.: Ocular Lesions of Boeck's Sarcoid, *Tr. Am. Ophth. Soc.* **37**:422-458, 1939. (c) Schultz, A.: Boeck's Sarcoid with Uveoparotitis and Dacryoadenitis, *Am. J. Ophth.* **28**:1010-1014, 1945. (d) Woods, A. C., and Guyton, J. S.: Role of Sarcoidosis and of Brucellosis in Uveitis, *Arch. Ophth.* **31**:469-480 (June) 1944. (e) Walsh, F. B.: Ocular Importance of Sarcoid: Its Relation to Uveoparotid Fever, *ibid.* **21**:421-438 (March) 1939.

antigen; blood counts; determination of the sedimentation rate; urinalysis; serum agglutination tests for typhoid, paratyphoid, tularemia, brucellosis and the rickettsial diseases; the Kahn tests, and stereoscopic roentgenographic examinations of the chest should also be made on patients with sarcoidosis in a search for other diseases.

*Thoracic Disease.*—Lesions in the chest are not necessarily characteristic, but they are probably the most frequent clinical sign and their proper interpretation is of great aid in the clinical diagnosis of sarcoidosis. The roentgenologist, however, must use the history and available clinical data for intelligent interpretation of the roentgenograms.

Two general types of thoracic lesions are associated with sarcoidosis. The first type is that of involvement of the hilar nodule, consisting of gross enlargement of the bronchial nodes, or less often, of the bifurcation of the paratracheal groups, with coarse radiations of dilated, deep lymphatic striae extending from the enlarged nodes toward the periphery of the lungs. These deep lymphatic vessels, unlike pulmonary vessels, seldom bifurcate and are denser, narrower and more sharply defined than are blood vessels. This peripheral prolongation of the striae is sometimes called fibrotic extension. The term is proper only in relation to the configuration of the density, and does not necessarily mean fibrosis of the lung in the sense of proliferated fibrous tissue. The fact that these pulmonary lesions often completely resolve is not in keeping with the impression of permanence of fibrous tissue. It is the opinion of roentgenologists in this clinic that one of the important features of extension from the hilar nodes in sarcoidosis, in contrast to tuberculous extension, is that it is quite uniformly bilateral, and that both pulmonary fields may be conspicuously involved in their central and lower parts, with sparing of the apexes. In tuberculosis it is rare to find widespread parenchymatous extension without invasion of the apexes.

In the second type of thoracic lesions the involvement of the hilar nodules is accompanied with or followed by widespread miliary lesions of irregular size throughout both lungs. If the hilar nodes are small, the picture may be similar to that of miliary tuberculosis, and may at times be impossible to differentiate by roentgenograms alone. The roentgenologist must correctly evaluate the degree of illness of the patient, the temperature curve, the sedimentation rate and other available clinical information. With this method, sarcoidosis or miliary tuberculosis may be considered probable or very unlikely.

The two types may be present at the same time. In some cases in which there are small hilar nodes and widespread miliary lesions with deep and superficial striations, the picture may be identical with miners' silicosis. It has been pointed out that gross enlargement of

diagnosis of sarcoidosis have died of proved terminal tuberculosis (case 4). The problem of the relation of sarcoidosis and tuberculosis cannot be dropped at this point, for it reappears frequently and provokingly throughout the various phases of the discussion and report of cases which follow.

#### DIAGNOSTIC PROCEDURES AND PROBLEMS

Physicians who are confronted with the problem of diagnosis of sarcoidosis usually depend on one or more of the following procedures to furnish clinical information: examination of the eyes; biopsies of the skin, lymph nodes and nasal mucosa, and roentgenographic studies of the chest and bones of the hands and feet. In clinical practice, then, the patient may be seen by several specialists, including the ophthalmologist, the otolaryngologist, the dermatologist, the chest clinician and the roentgenologist, with the general pathologist often giving an additional opinion on biopsied material. The procedure and some of the problems of diagnosis pertaining to each specialty will be discussed before an attempt is made to analyze the 10 cases reported.

*Ocular Disease.*—The patient with sarcoidosis is seldom acutely ill; the cutaneous lesions are not painful and seldom disfiguring, and the thoracic condition is usually unsuspected. The eyes, however, may be painful; vision may be blurred, or at least the ocular disease may be severe enough to cause the patient to seek medical advice.

Briefly, an examination of the eye may reveal any combination of nodules of the lids, conjunctivitis, keratitis, iritis, iridocyclitis and, rarely, chorioretinitis, with any of the possible symptoms and complications of these conditions. The severest and most obvious feature is generally iritis<sup>11</sup> of the nodular or seroplastic type, with extensive posterior synechias, and there is an abundance of the keratic precipitates of the mutton fat type. In this series of cases, keratitis was a common condition. The eye may be painful in the acute stage, or it may be painless with the insidious onset of the disease. Chronicity following either the stormy or the insidious beginning is the almost invariable course.

Only a description of the disease and a diagnosis of nodular iritis related to a granulomatous disease, or of seroplastic iritis of unknown cause, may be given, for the initial ocular inspection reveals little of aid in differential diagnosis. Most ophthalmologists agree that there may be only a suggestion that the causative factor lies in a granulomatous disease. In the presence of the more obvious lesions of the skin, and possibly of some enlarged lymph nodes, sarcoidosis should be suspected and considered. Intradermal tests with old tuberculin and brucella

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11. Guyton and Woods.<sup>42</sup> Levitt, J. M.: Boeck's Sarcoid with Ocular Localization: Survey of the Literature and Report of a Case, *Arch. Ophth.* 26:358-388 (Sept. 4) 1941.

out lesions with rather sharp borders, and they appear to be located in the exact center of the metaphysis of the bone and do not invade the cortex. Before the advent of popularity of the diagnosis of sarcoidosis these punched-out lesions of bone were called tuberculosis osteitis cystica (cases 4 and 10).

*Disease of the Nasal Mucosa.*—The rhinologists in this clinic have found that histologic evidence of sarcoid or tuberculosis is extremely rare in the mucous membrane of the nose and accessory sinuses. In a series of biopsies in presumptive cases of sarcoidosis, histologic sections that particularly resemble sarcoid granulomas were not observed. The usual report was chronic inflammatory tissue, with hypertrophy of the mucosa, which was richly supplied with mucin glands. There were sometimes groups of epithelioid cells, but any grouping of these cells into well organized tubercles resembling either tuberculosis or sarcoid was rare; in fact, small tubercle-like whorls were noted in only 1 case of the series. Several factors may account for this picture: The nasal mucosa may be resistant to invasion by or reaction to the tubercle bacillus. The tissue structure may be such that it does not lend itself to formation of tubercles or sarcoid granulomas. Other bacterial reactions, in the form of secondary invaders, may distort and inhibit granulomatous formation.

*Cutaneous Lesions.*—The gross description of the cutaneous lesions falls into three types, with additional variations for the Negro<sup>13</sup>:

1. Disseminated miliary sarcoidosis (Boeck) is an eruption of firm nodules which may be found on any surface of the body. Occurring in small numbers, usually on the face, arms, shoulders or hands, these nodules vary in size and shape and are brownish red or purplish. Under pressure, they appear as grayish yellow macules in the skin. If they heal, atrophic scars are formed.

2. In subcutaneous sarcoidosis (Darier-Roussy sarcoid<sup>14</sup>), the nodules are subcutaneous, and the skin may be freely movable over them. They are round and several centimeters in diameter and feel like soft shot under the skin. They may be located anywhere on the body, singly or in groups, sometimes forming plaques. The color is that of the skin, there being occasionally a bluish discoloration of the skin over the nodules.

3. In lupus pernio, superficial lesions affect the nose, cheeks, ears, hands and feet. These lesions appear as infiltrating, bluish

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13. (a) Bloom, D., and Mendelsohn, H.: Cutaneous Tuberculosis in the Negro: A Clinical Entity, *Arch. Dermat. & Syph.* **36**:937-951 (Nov.) 1937. (b) Nomland, R.: Hematogenous Cutaneous Tuberculosis (Sarcoid) in Negroes, *ibid.* **30**:59-75 (July) 1934.

14. Maloney, E. R., and Combes, F. C.: Darier-Roussy's Sarcoid, *Arch. Dermat. & Syph.* **33**:709-724 (April) 1936.



the bronchial glands is rare with miliary tuberculosis, except in the Negro, and that it is unknown in miners' silicosis. Possible exposure to high concentrations of silica dust should, of course, be considered in the history.

Roentgenographic differential diagnosis of sarcoidosis and late Hodgkin's disease or lymphoblastoma may also be impossible. Here, again, other clinical factors, such as a blood dyscrasia, histologic changes in a lymph node or enlargement of the spleen, may help to identify the disease. If other clinical signs of Hodgkin's disease or lymphoblastoma are lacking, a trial of high voltage roentgen irradiation of the hilar nodes may safely be attempted, for it is well known that these diseases are sensitive to radiation and, if they are present, the resolution of the pulmonary lesions is often dramatic. Pohle, Paul and Clark<sup>12</sup> reported 14 cases in which high voltage irradiation to the hilar region of patients with sarcoidosis was attended with no untoward results. In fact, it is the authors' impression that in 6 of the cases slight improvement occurred, but nothing similar to the results obtained with Hodgkin's disease.

The roentgenographic picture of sarcoidosis may further be confused by the presence of calcified nodes, pleural thickening, effusions or even cavitations. Without previous roentgenograms, it is not possible to determine whether the sarcoidosis is superimposed on old tuberculous lesions or is the present active disease. It is not believed that calcifications, effusions or cavitations are part of the pulmonary picture of sarcoidosis, but their presence before lesions of sarcoidosis occur make the picture more like tuberculosis than sarcoidosis. These complications are mentioned to show the difficulties that may be encountered in diagnosis of sarcoidosis of the chest. It is not surprising that the roentgenologist may frequently report tuberculosis of the chest rather than sarcoidosis. The experience in this clinic is that either tuberculosis or Hodgkin's disease is often the first roentgenographic diagnosis, rather than sarcoidosis. If the lesions of the chest were uniformly typical of one or the other of the two types mentioned, the roentgenologist's problem would be greatly simplified.

*Lesions of Bone.*—Roentgenographic evidence of lesions of bone is considered to be valuable as a diagnostic clue to sarcoidosis. Unfortunately, these lesions are not common. Woods and Guyton<sup>4d</sup> stated that lesions of bone occur in about 10 per cent of reported cases; however, none were observed in their 15 cases. The typical lesions are observed in the metaphyses of the phalanges and in the metacarpal bones of the hands and feet. They are definite, punched-

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12. Pohle, E. A.; Paul, L. W., and Clark, E. A.: Roentgen Therapy of Boeck's Sarcoid, *Am. J. M. Sc.* **209**:503-513, 1945.

*Biopsy of Lymph Nodes.*—The microscopic structure of sarcoidosis of the lymph nodes is not so uniform as that of the cutaneous lesion. The tissue of the lymph node is apt to have a confusing number of lymphocytes and giant cells; collagenous trabeculae are usually absent. The picture is not easily confused with tuberculosis, but differential diagnosis is often impossible. A feature of sarcoid of lymph nodes, pointed out by Dr. Eleanor Humphreys, of the University of Chicago, is that the epithelioid whorls often surround a small central vessel. This picture is never seen with tuberculosis, since central necrosis is frequent in tuberculous lymph nodes and could hardly occur with a functioning central vessel. Great variations in individual lymph nodes from the same patient also exist, and excellent examples of sarcoid adenitis and tuberculous adenitis in a patient with proved tuberculosis have been observed.

*Mantoux Test.*—A negative result in the Mantoux test is of value in the diagnosis of sarcoidosis; however, evaluation of the significance of the reactions is somewhat in doubt. In this clinic, every patient suspected of having sarcoidosis is given an intradermal injection of 0.1 cc. of a suspension of old tuberculin U. S. P. in saline solution<sup>4d</sup> in a dilution of 1:100,000, the dilutions being increased through strengths 1:10,000, 1:1,000, 1:100 and 1:10 to an undiluted suspension. The reactions are evaluated at the end of twenty-four, forty-eight and seventy-two hours. Some of the patients with sarcoidosis show no reaction even to the undiluted old tuberculin, and Woods and Guyton carried out this test with 10 cc. of undiluted old tuberculin without reaction in some of their cases. In all but 1 of the cases reported in this paper the cutaneous reactions were negative to dilutions of 1:1,000, and most patients were insensitive to stronger concentrations. The meaning of this is not clear, but in this clinic the arbitrary acceptance of a positive cutaneous reaction to a 1:100 dilution is compatible with a diagnosis of sarcoidosis, whereas a positive reaction to a dilution of 1:1,000 is considered questionable.

#### REPORT OF CASES

CASE 1.—J. J., a Negro housewife aged 25, was first seen in the eye clinic in March 1946. The patient complained of decreased vision and a growth in the left eye; she had discovered the growth in December 1944 on looking into a mirror; a short time prior to discovery of the tumor the left eye had been painful, but since December 1944 it had been painless. The patient had otherwise been well.

During the nine months following the ocular symptoms she had tremor of the hands, fatigue and pronounced early muscular weakness. There was no cough or fever. The condition was diagnosed by a physician as a "nervous breakdown." A routine industrial roentgenogram of the chest in the spring of 1944 revealed nothing noteworthy. The patient had had an obstruction of the left nostril since

or violaceous plaques. The surface shows a well marked network of dilated blood vessels. In the Negro, any of these three types of lesions may be found, in addition to superficial scaling plaques and superficial nodules about the mouth, nose, eyelids and brow.

Biopsy of the skin, with microscopic examination of the stained sections, is also an aid in diagnosis of sarcoidosis.<sup>15</sup> The structure of the skin seems to lend itself to more uniformity in the microscopic appearance of sarcoid lesions than any other tissue of the body. For that reason, perhaps, dermatopathologists feel more certain of their diagnosis of sarcoidosis than do pathologists dealing with other tissue. The more typical lesions of sarcoidosis are described as very compact, small whorls of distinct epithelioid cells, without evidence of central necrosis and with few giant cells and a very sparse surrounding mantle of lymphocytes, or more typically the lymphocytes may be absent. The conglomerate whorls are spaced and surrounded by heavy and distinct connective tissue trabeculae of collagenous fibers, which are indicative of the disease. No organisms are found. Woods and Guyton<sup>4d</sup> stated that in 20 per cent of cases peculiar, hematoxylin-staining, usually doubly refractile inclusions, known as Schaumann bodies, are seen in the giant cells; but if Schaumann bodies are not present, it is impossible to differentiate lesions of sarcoidosis histologically from the hard tubercles of tuberculosis. The picture in histologic sections of the skin is, unfortunately, not an infallible test, for not all sections are typical.

The case described by Ronchese<sup>3c</sup> is an excellent illustration of the diverse opinion of dermatopathologists in the microscopic differential diagnosis of Boeck's sarcoidosis and lupus vulgaris (tuberculosis). A histologic section, a clinical photograph and a brief summary of the history in this case were sent to 10 eminent dermatopathologists; 6 favored the diagnosis of sarcoidosis, and 2 the diagnosis of lupus vulgaris; 2 stated that the picture was consistent with either sarcoidosis or lupus vulgaris. The opinions of the roentgenologists in regard to the roentgenograms of the chest were likewise almost equally divided between sarcoidosis and miliary tuberculosis. The autopsy in this case, held within seven months of examination of the microscopic sections and the roentgenograms of the chest, was reported by Dr. F. E. Katzman and Dr. R. J. Williams to reveal the presence of typical acid-fast bacilli in the lesions of the lung, spleen and heart, confirming the diagnosis of miliary tuberculosis.

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15. Longcope.<sup>7a</sup> Longcope and Pierson.<sup>7b</sup> Nomland.<sup>13b</sup> Jordon, J. W., and Osborne, E. D.: Besnier-Boeck's Disease, *Arch. Dermat. & Syph.* **35**:663-684 (April) 1937. Laymon, C. W., and Michelson, H. E.: The Micropapular Tubercloid, *ibid.* **42**:625-640 (Oct.) 1940. Montgomery, H.: Histopathology of Various Types of Cutaneous Tuberculosis, *ibid.* **35**:698-715 (April) 1937.

*Diagnostic Criteria.*—The patient had nodular iritis and cutaneous lesions of the Darier-Roussy type. Microscopically, the cutaneous lesions were compatible with, but not typical of, sarcoidosis. Roentgenograms of the chest in the absence of other clinical signs of Hodgkin's disease and malignant growth were compatible with the hilar type of sarcoidosis, especially since the cutaneous tests gave negative reactions to 0.1 cc. of undiluted old tuberculin. The nodular iritis could not be differentiated from other granulomatous diseases, particularly tuberculosis. In this case, the roentgenograms of the chest and the general clinical picture were considered as of the most diagnostic value, with cutaneous lesions, biopsy observa-

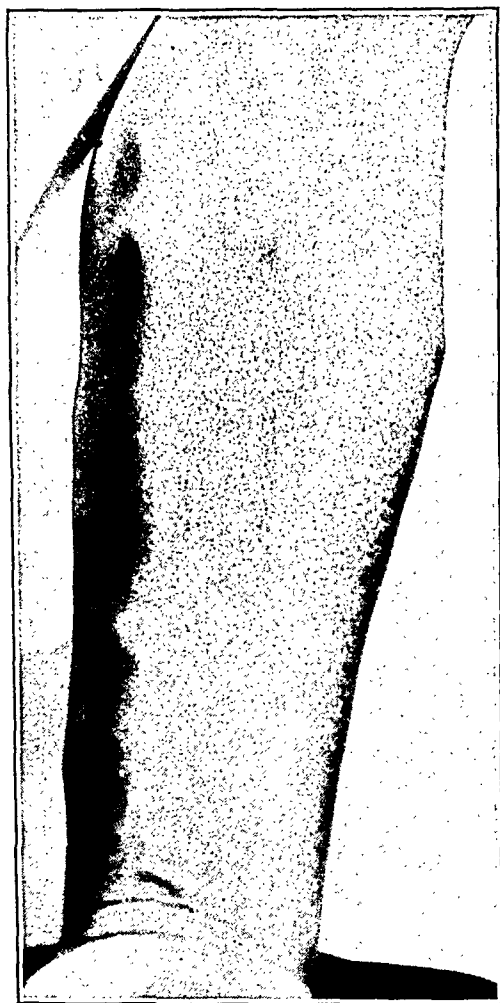


Fig. 1 (case 1).—Flexor surface of forearm, showing subcutaneous nodules of the Darier-Roussy type of Boeck's sarcoidosis (March 1946).

tions on the skin, the negative reaction to tuberculin and the nodular iritis of importance, in approximately that order.

CASE 2.—Mrs. M. B., a white woman aged 59, a rooming house keeper, was first seen in the eye clinic in February 1947. She complained of black spots before her eyes, ocular burning and itching, and a yellow, sticky secretion of three months' duration. There had been no periods of weakness, loss of weight, cough or fever. Moderately severe diabetes had been discovered one year before, when the patient became suspicious of polyuria. The diabetes was controlled with modified diet and administration of 15 units of protamine zinc insulin three times daily. Her family history was negative for tuberculosis, and she had had no contact with the disease.

March 1944, with pain over the left maxillary sinus. She had had the usual childhood diseases; the family history was noncontributory except that the patient's mother was said to have died of tuberculosis at the age of 36.

A brief summary of results of the ophthalmologic examination follows. Vision was 20/16 in the right eye and 20/100 in the left. The right eye was not diseased. In the left eye a large, yellowish pink tumor was to be seen growing up from the iris and filling about one fourth of the anterior chamber. The tumor extended in a circular manner at the limbus from 6 to 9 o'clock. In this sector it filled the angle of the anterior chamber, and the anterior surface of the tumor in places pressed against, but was not attached to, the cornea. The surface of the tumor was slightly lobulated and was covered with a fine network of capillaries, arising from the iris but not from the deep portion of the limbus or the cornea. The pupil was bound down with ringlike posterior synechias, and the pupillary aperture was covered with a thin gray membrane. The aqueous showed a moderately increased flare and a few floating cells; the cornea was clear except for a large number of keratic precipitates on the endothelium of mutton fat type. The fundus appeared normal. Intraocular tension (Schiotz) was normal in both eyes.

Three weeks after the first examination a rare opportunity was afforded us to observe the beginning of sarcoid iritis in the right eye. The first sign recognized on observation with the slit lamp was beginning exfoliation of the iris pigment at the pupillary border. A small increase in the aqueous flare next developed, and then three tiny nodules were seen beneath the anterior surface of the iris, two being located near the limbus and one near the pupillary border. During the next two weeks the nodules increased slowly in size; a few cells appeared in the aqueous; the flare increased, and, last, the keratic precipitates of mutton fat type appeared in considerable numbers. The final picture was one of nodular iritis with the Koepe nodules, which were light gray, round and about 1 mm. in diameter and 0.5 mm. in height.

Roentgenograms of the chest showed infiltration of the hilar regions, with extension along the superior mediastinum and into both upper lobes, the distribution suggesting sarcoid disease. Roentgenograms of the bones of the hands and feet were normal.

Several small subcutaneous masses, 5 to 8 mm. in diameter, were found on the flexor surfaces of the arms and in the left cervical region. The skin was freely movable over the lesions, a condition resembling the Darier-Roussy sarcoid (fig. 1). Biopsy of a subcutaneous nodule revealed a mass of highly vascularized granulation tissue, in which epithelioid cells were occasionally arranged to form tuberculoid structures with a few Langhans giant cells. No caseation necrosis was seen. The total picture was compatible with sarcoidosis.

Routine laboratory tests gave normal results. The Kahn test and intradermal injections of old tuberculin in dilutions up to, and including, 0.1 cc. of undiluted suspension gave negative reactions. Biopsy of the nasal polyps revealed no evidence of sarcoid tissue. Roentgen therapy was tried for the tumor of the iris; after four treatments the mass appeared slightly shrunken, but again increased in size during the subsequent six treatments. The patient was last observed in August 1946. The tumor of the iris was of the same size. Vision was 20/16 in the right eye and was limited to perception of hand movements in the left eye.

In April 1947 the patient died at another hospital, after several weeks of severe weakness. The cause of death was given as tuberculous meningitis on the basis of neurologic findings of meningeal irritation, stupor leading to coma and one doubtful report of tubercle bacilli in the sputum.

Roentgenograms of the chest which suggested, but were not typical of, sarcoidosis and a negative cutaneous reaction to old tuberculin in a dilution of 1:1,000 were added factors influencing the diagnosis. The cutaneous sensitivity tests were not carried further because empiric tuberculin therapy was instituted before a diagnosis of sarcoidosis was made. In this case, the biopsy of the skin and the cutaneous lesions were considered the most important diagnostic features, with the negative reaction to old tuberculin, the roentgenograms of the chest and the iritis of importance approximately in that order.

CASE 3.—Dr. R., a Negro housewife aged 36, was seen in the eye clinic in July 1946. She gave a history of redness and burning of the right eye, which began in September 1946. The condition of the eye improved for a few months, but seven months later it became worse, at which time the left eye also became red. In June 1946 roentgenograms of the chest and biopsy of a cervical lymph node were reported as showing typical signs of Boeck's sarcoidosis. The patient gave no history of serious or chronic illness before her ocular symptoms began. During the past fifteen months she had lost 20 pounds (9.1 Kg.) in weight but had no cough, fever or feeling of fatigue. Several brothers and sisters of the patient's mother were said to have died of tuberculosis, but they had had no direct contact with this patient. The family history was otherwise not significant.

The ophthalmologic examination showed vision of 20/70 in the right eye and 20/25 in the left eye. The conjunctiva of the right eye was moderately injected. The corneal epithelium and stroma were clear. There were a few round, mutton fat keratic precipitates on the corneal endothelium, a moderate increase in aqueous flare and 5 to 6 floating cells per smallest pinhole field of the slit lamp. No new vessels or nodules were seen in the iris. The pupil was held to a diameter of 2.5 mm. by numerous heavy posterior ring synechias. The anterior capsule of the lens showed well scattered deposits of brown pigment, and the pupil was covered with a thin gray veil continuous with the ring synechia. The left eye presented a picture similar to that of the right eye, with smooth conjunctival injection, clear cornea, mutton fat keratic precipitates, aqueous flare, cells and synechias, all in slightly lesser amounts. Both lenses were clear, and the fundi were normal. The interocular tension (Schiotz) was normal in each eye.

Roentgenograms of the chest showed moderate enlargement of the mediastinal lymph nodes, the largest node measuring 4 cm. The pulmonary fields were otherwise clear. The clinical diagnosis was moderate hilar lymphadenopathy, compatible with sarcoidosis. Roentgenograms of the small bones of the hands and feet revealed no disease. An intradermal test gave a negative reaction to 0.1 cc. of undiluted old tuberculin. The ears, nose and throat were normal, and no cutaneous lesions were present. A few cervical lymph nodes were palpable. Routine laboratory tests gave normal results, and the Kahn reaction was negative. The eyes improved spontaneously, beginning in September 1946, but one year later both eyes again became worse. The patient became acutely ill, with severe weakness and further loss of weight, but without fever or cough. Vision in October 1947 was still 20/40 in each eye.

*Diagnostic Criteria.*—The patient had a seroplastic type of iritis. The lesions of the chest were indicative of sarcoid disease, in view of the negative cutaneous reaction to undiluted old tuberculin. The results of biopsy of a lymph node contributed to the impression of sarcoidosis. In this case, roentgenograms of the chest and the negative reaction to tuberculin were considered primary evidence in the diagnosis. Biopsy of a lymph node gave information of secondary importance because of the usual difficulty in differentiating sarcoidosis and tuberculosis in the lymph node. Iritis was considered of least value.

Vision was 20/40 in the right eye and 20/25 in the left eye. The conjunctivas were moderately injected. The substance of the right cornea was clear. On the corneal endothelium were numerous round keratic precipitates of the mutton fat type. The aqueous showed a moderately increased flare and occasional floating cells. The iris was edematous, but without nodules. The right pupil dilated to 0.5 mm. with atropine, without evidence of synechias. The left eye was normal. Both fundi were clearly seen; no abnormality was noted other than moderate sclerotic changes of the retinal vessels. The intraocular tension (Schiotz) was within normal limits in each eye. Routine laboratory tests gave normal results, and the reaction to the Kahn test was negative.

The first stereoroentgenograms of the chest were reported to show minimal hilar calcification and normal lung fields, with evidence of minimal healed

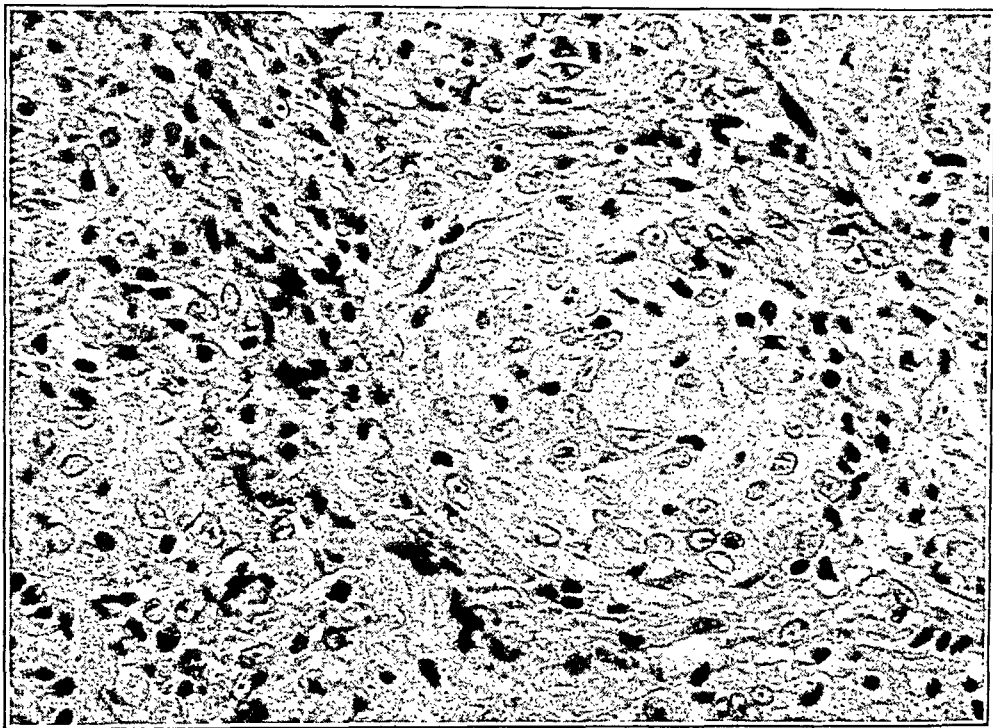


Fig. 2 (case 2).—Biopsy specimen of the skin, showing multiple whorls of epithelioid cells, with noncaseating centers and scant lymphocytes, highly suggestive of Boeck's sarcoidosis;  $\times 460$  (April 1947).

tuberculosis. The impression was that of iritis, tuberculous type. The reaction to intradermal injection of old tuberculin in a dilution of 1:1,000 was negative. Within a few weeks a bluish discoloration was noticed on the end of the patient's nose. The dermatologist diagnosed the lesion as sarcoidosis of the lupus pernio type and confirmed this diagnosis by biopsy of a specimen from the skin of the nose (fig. 2). In a review of the roentgenograms of the chest by another roentgenologist, one very large, soft hilar gland, measuring over 1 inch (2.5 cm.) in diameter, was seen. The lesion was reported as probably very early sarcoid. For nine months no appreciable change occurred in the patient's condition.

*Diagnostic Criteria.*—This patient had seroplastic iritis and cutaneous lesions of the lupus pernio type, with biopsied material strongly indicative of sarcoidosis.

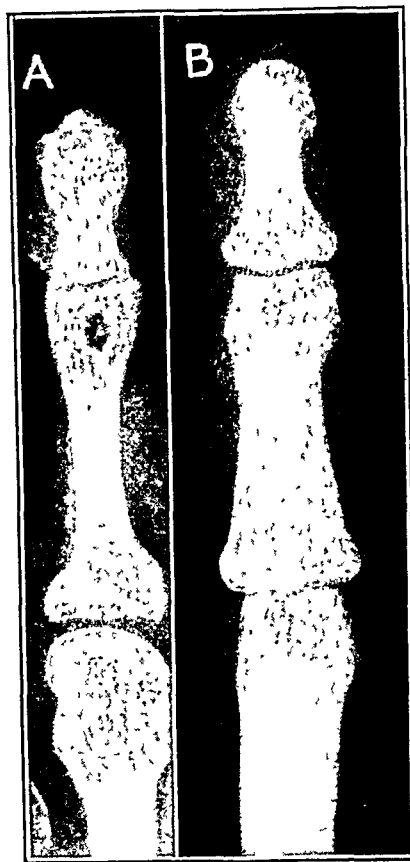


Fig. 3 (case 4).—*A*, rarefaction of bone in toe, and, *B*, rarefaction of bone in finger, both highly suggestive of Boeck's sarcoidosis (January 1947).

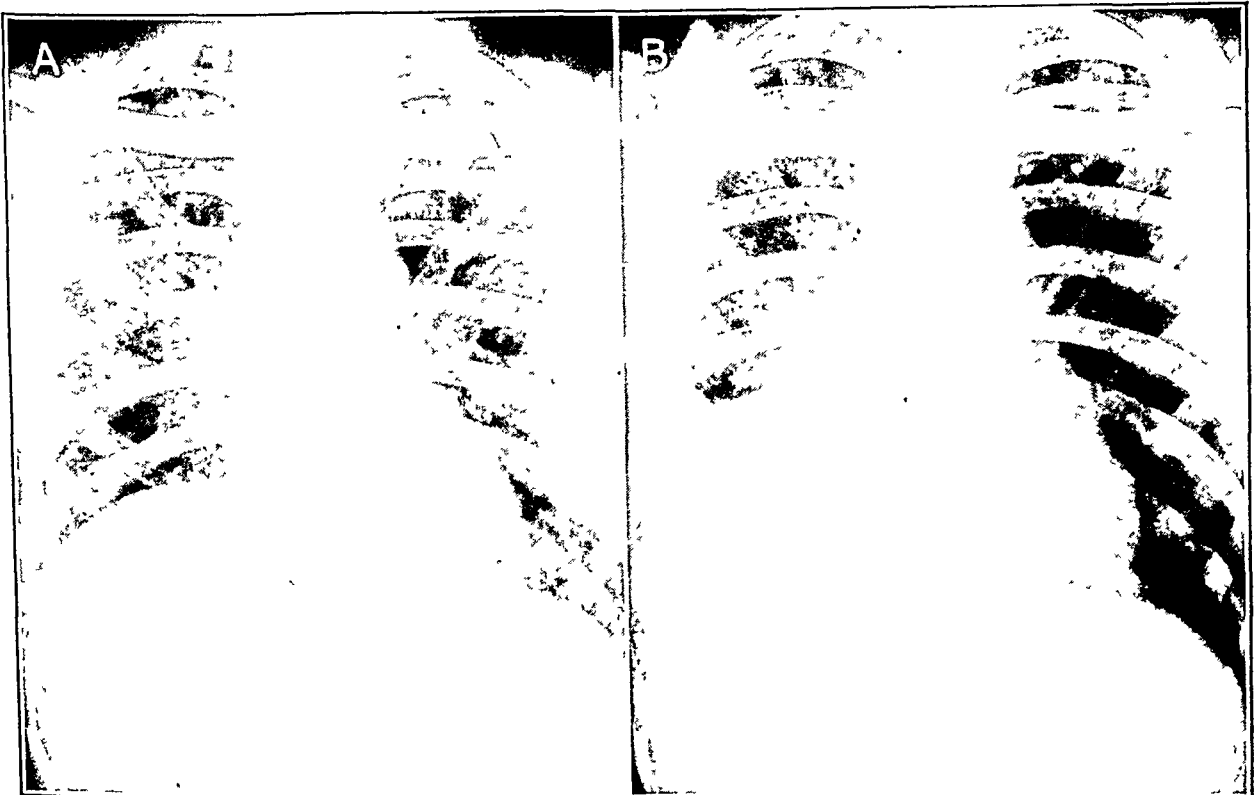


Fig. 4 (case 4).—*A*, roentgenogram of the chest (August 1947), suggestive of tuberculosis but compatible with Boeck's sarcoidosis; *B*, roentgenogram of the same chest as that shown in *A*, taken two weeks later, now showing right pleural effusion, suggestive of tuberculosis, and not of Boeck's sarcoidosis.



CASE 4.—J. W., a Negro laborer aged 27, first seen in the eye clinic in January 1947, gave a history of illness beginning two years before with pain, tearing and gradual decrease in vision in the left eye. Nodules appeared in the skin of both upper eyelids. A short time later, nodules the size of a pea were found in the skin of the neck, arms and legs. The patient gave no history of chronic cough, fever, loss of weight or fatigue. His past and family histories were noncontributory.

On examination, many intracutaneous papules of the face and eyelids were seen. The upper lids were thickened. The right conjunctiva was smooth, hyperemic and free of follicles. The upper fifth of the cornea showed a sclerosing keratitis, the opacities extending through all layers, and was infiltrated with superficial pannus of the same extent as the sclerosis. Examination with the slit lamp demonstrated no changes in the aqueous, iris or lens.

There was severe photophobia of the left eye. There were three yellow follicles, 1 mm. in diameter, with red borders on the conjunctiva of the upper lid, but the remaining conjunctival surface was intensely hyperemic. A deep vascularized keratitis and a macular opacity covered most of the cornea. The aqueous appeared clear; the atrophic iris had an annular synechia, and the lens was densely cataractous. The right fundus appeared normal. Vision was 20/16 in the right eye and was limited to light perception in the left eye. The intraocular tension (Schiotz) was normal in each eye.

Roentgenograms of the hands and feet showed an abnormal condition. Round areas of decreased density were seen in the metaphysial region of the distal end of the second phalanx of the third toe of the left foot (fig. 3 A); in the proximal metaphysial region of the middle phalanx of the fourth finger of the left hand (fig. 3 B), and in the distal phalanx of the same finger and that of the third digit. The impression was that of Boeck's sarcoidosis of the phalanges of both hands and feet. The roentgenograms of the chest revealed the presence of irregular, soft, fibrous infiltrations scattered throughout both lungs, with minimal bilateral thickening of the apical pleura and a suggestion of cavity formation in the lateral aspect of the upper lobe of the right lung near the fifth interspace (fig. 4 A). The impression was that of widespread pulmonary infiltration with questionable cavitation of the upper lobe of the right lung. From the roentgenologic standpoint, this evidence was compatible with tuberculosis, but, because of the lesions of the eyes, skin and bones, it was decided that the disease should be called sarcoidosis. The patient had a strong reaction to old tuberculin in a dilution of 1:1,000. The laboratory tests all gave results within normal limits, the Wassermann reactions of the blood and spinal fluid were negative, and the colloidal gold curve was normal. In August 1947, roentgenograms showed only an increase in pleural thickening and no change in osseous rarefactions in the hands and feet.

In the same month the patient entered the hospital acutely ill with severe pain in the chest and high, spiking fever. Physical examination and roentgenograms of the chest (fig. 4 B) showed a large pleural effusion, which was regarded as tuberculous. However, acid-fast organisms were not found on inoculation of guinea pigs with the aspirated fluid, nor were the bacilli found in repeated examinations of the sputum and stomach washings. The sensitivity of the skin to a 1:1,000 dilution of old tuberculin persisted. The chest clinicians, nevertheless, felt that the patient had terminal tuberculosis. On Sept. 19, 1947, tubercle bacilli were obtained by smear and culture of material from a caseous axillary lymph node.

*Diagnostic Criteria.*—This case was most interesting from a diagnostic viewpoint. Anterior uveitis, keratitis and cutaneous lesions clinically compatible with

In April 1947 the ocular disease was still active. Vision in the right eye was limited to light perception with poor projection; that in the left eye was increased to 8/200. Corneal opacities were unchanged, and numerous keratic precipitates were still present. Routine intradermal tests gave negative reactions.

*Diagnostic Criteria.*—The patient had widespread lesions of the skin, clinically diagnosed as sarcoid disease. The roentgenograms of the chest suggested sarcoidosis, particularly in view of the negative cutaneous reaction to undiluted old tuberculin. The patient also had keratitis, iritis and osseous lesions suggestive of sarcoidosis. The roentgenograms of the chest, the negative reaction to tuberculin



Fig. 5 (case 5).—Lupus pernio type of Boeck's sarcoidosis, involving the lids, nose, mouth and other portions of the face (March 1946).

and the lesions of bone were considered most indicative of the disease. Permission for biopsy of the skin was not granted.

CASE 6.—M. R., an obese Negro housewife aged 40, was first seen in the eye clinic in October 1945. She complained of bronchial asthma of seven years' duration, sinus trouble of four or five years' duration and cutaneous lesions of two years' duration. The lesions of the skin began on the upper portion of the arms and the shoulders, then spread to the back and later over the entire body. At first the lesions were flat, round or ovoid; later they became more irregular in shape, more elevated and larger, and some oozed a clear fluid. In 1942 the patient

sarcoidosis were observed. The roentgenograms of the chest were equivocal, and the skin was sensitive to old tuberculin in a dilution of 1:1,000. The bones had the punched-out rarefactions supposedly typical of Bøeck's sarcoidosis. Although the patient's disease was diagnosed as presumable sarcoidosis on this basis, the later clinical course and the demonstration of acid-fast organisms on smear, and culture of a lymph node confirmed the diagnosis of tuberculous lymphadenitis. It is possible that in this case sarcoidosis evolved into tuberculosis, or that tuberculosis was superimposed on sarcoid disease. However, it is most probable that in this case tuberculosis was misdiagnosed as sarcoidosis and, even more important, that the changes in the bones of the hands and feet, said to be typical of sarcoidosis, do not constitute a reliable diagnostic criterion. The ocular disease was probably also tuberculous.

CASE 5.—L. M., a white woman aged 45, unemployed, was first seen in 1945 in the clinic for diseases of the chest, from which she was referred to the eye clinic. She had had a chronic cough for one year and failing vision for thirteen months. For the past thirteen years she had had widespread lesions of the skin, which involved the face, lids, nose, arms and hands (fig. 5). The cutaneous lesions first appeared as nodules and later turned dark red; some ulcerated and took as long as eight months to heal. They were diagnosed as lesions of sarcoidosis. She stated that thirteen years before, when ulcers first appeared on the arms, her eyes had been sore and red for three months, and then all ocular symptoms had disappeared. About thirteen months prior to admission vision failed rapidly, and on examination she was able to see only patches of light and dark. The past and family histories were noncontributory.

Vision in the right eye was limited to perception of hand movements at 3 feet (90 cm.) and was 20/800 in the left eye. The middle thirds of the lids were badly scarred and notched. A heavy white mucoid exudate was present in each eye. The cilia were missing from the central third of both upper lids. The lids had a brawny edema. The light reflex from the corneal surfaces was "pebbly." Gray mottling involved all layers of the cornea; it was greater in the anterior and middle thirds and faded out toward Descemet's membrane. A moderate aqueous flare was present in each eye. The pupils were entopic, measured 1.5 mm. in diameter and were fixed by thick posterior synechias. Numerous mutton fat keratic precipitates were found on the corneas. No details of the lens or fundus could be seen in the right eye, and no red reflex was visible with the ophthalmoscope. A dull red fundic reflex was present in the left eye. Intraocular tension (Schiotz) was normal.

An intradermal test gave a negative reaction to 0.1 cc. of undiluted old tuberculin. Routine laboratory tests gave normal results, and the Kahn reaction was negative. Roentgenograms of the hands and feet disclosed rarefactions suggestive of sarcoid disease in the metaphysial regions of the second digit of the right foot and of the second, third and fourth digits of the right hand. Roentgenograms of the sinuses showed a fluid level in the right maxillary sinus. The floor of the left maxillary sinus was obscured, possibly by thick exudate. In the roentgenograms of the chest, a fine fibrotic mottling, extending from the hilus to the periphery of the lung, was present bilaterally, being more marked in the lower lobes. Some calcification was present in the hilus. Repeated roentgenograms of the chest over a period of two years showed a slight, but definite, increase in the amount of pulmonary fibrosis, with formation of multiple fine, rather dense nodulations through the middle third of each lung. This picture was compatible with sarcoid disease. Biopsy of the nasal mucosa revealed hyperplasia of epithelium and a nest of tubercle-like tissue of unknown origin.

Two days after this visit the patient noticed a white mark on her left cornea. On examination it proved to be a white opacity, measuring 1 by 1.5 mm., leukomatous in density and involving the superficial third of the corneal substance, with similar, but small, opacities at 7, 8 and 9 o'clock near the limbus. The cornea did not stain with fluorescein. There was a slight increase in aqueous ray, but no floating cells, edema of the iris or exfoliation of pigment that might indicate beginning uveitis. The diagnosis was keratoconjunctivitis. Smears and culture were free of organisms.

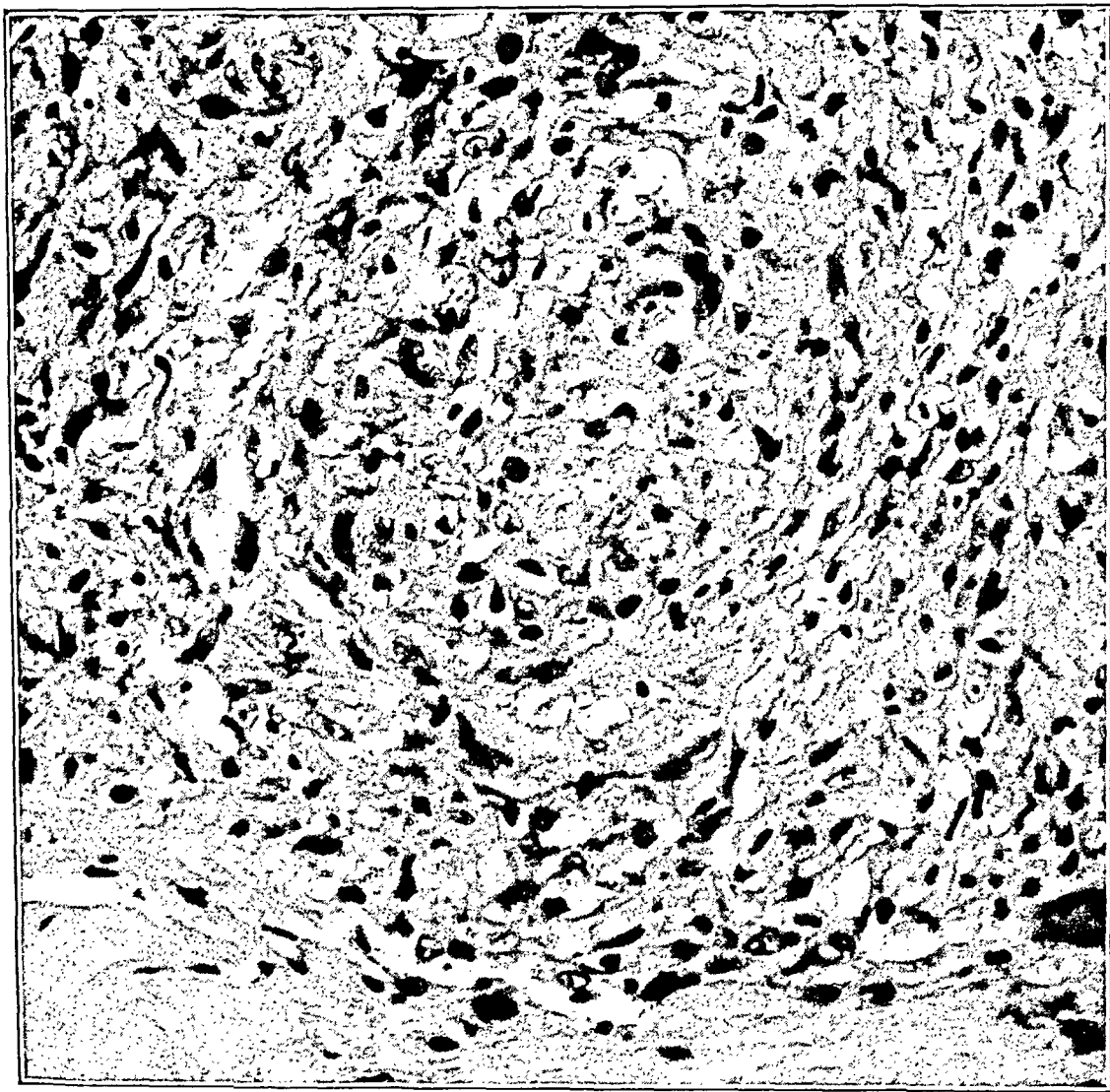


Fig. 6 (case 7).—Biopsy specimen (July 1946) of the skin, showing a non-caseating, closely packed, epithelioid whorl lying adjacent to fatty tissue;  $\times 460$ .

Two months later the patient came in complaining of pain and redness of the left eye. The aqueous flare had increased to 3 plus; an occasional floating cell, but no keratic precipitates, were seen. Within another month severe exudative and plastic iritis developed in both eyes. Innumerable cells were found in the aqueous, and many fatty keratic precipitates, abundant posterior synechias and fibrin-like deposits were seen on the lenticular capsules. No Koeppe nodules were observed. The opacities of the left cornea were unchanged. The right cornea

began to have severe orbital and temporal headaches, with associated burning of the eyes, a discharge and redness. In 1943 there developed a persistent chronic cough, productive of gray sputum. There was no history of fever. In 1944 she had severe sinusitis, until a transnasal operation gave pronounced symptomatic relief. The patient still complained of a scratchy sensation in both eyes, but no actual pain. There had been a loss in weight of 15 to 20 pounds (6.8 to 9.1 Kg.) in the past two years. The family history was noncontributory.

Ocular examination revealed vision of 20/20 in the right eye and 20/200 in the left eye. A left divergent squint of 30 degrees was present. The conjunctivas were moderately hyperemic. The palpebral conjunctivas were granular as the result of numerous elevated, yellow follicles. Ophthalmoscopic study and examination with the slit lamp revealed no evidence of past or present uveitis. The intraocular tension (Schiotz) was normal. The symptoms of conjunctivitis increased during the course of later visits. The tarsal conjunctiva became intensely red and covered with numerous tiny hemorrhages, follicles and scars. An early superficial pannus developed on the upper third of the left cornea, with no other evidence of keratitis. Extensive bacteriologic investigation for organisms and inclusion bodies was unsuccessful. After trial use of many common antiseptics, the conjunctiva cleared dramatically with application of a 1 per cent solution of silver nitrate. The pannus, however, persisted.

Biopsy of the nasal mucosa showed bilateral polyposis, unrelated to sarcoidosis. The brown macular lesions of the skin of the face and other parts of the body were irregular in size and were superficially scarred and desquamated. Biopsy of the skin by an eminent pathologist showed tissue similar to that of Boeck's sarcoidosis. Intradermal tests with old tuberculin in a dilution of 1:100 gave a definitely positive reaction. Roentgenograms of the chest showed widespread fibrosis, most marked in both apexes, and multiple calcifications in both hili, with two small, discrete areas of calcification in the periphery of the lower part of the right lung. The impression was that the pulmonary disease was more typical of tuberculosis than of sarcoidosis. Roentgenograms of the hands and feet revealed no lesions. Routine laboratory intradermal tests gave negative reactions.

*Diagnostic Criteria.*—The patient had conjunctivitis and keratitis with pannus, without uveitis. The lesions of the skin were diagnosed as sarcoidosis, and the roentgenograms of the chest were compatible with the picture of sarcoidosis. The cutaneous reaction to a 1:100 dilution of old tuberculin was positive. The biopsy of the skin was assumed to show lesions of diagnostic importance, and the roentgenographic changes in the chest, coupled with low cutaneous sensitivity to tuberculin, gave additional evidence. The correct interpretation of a positive reaction to intradermal injection of 0.1 cc. of old tuberculin U. S. P. was not clear.

CASE 7.—G. A., a Negro housewife aged 30, was first seen in the eye clinic in July 1946. The patient stated that she had had a lesion of the skin for several years, but had had no ocular trouble until three days prior to her first visit. At that time the left eye became red and had a scratchy sensation. There was no history of serious or chronic illness, cough, fever or loss of weight. The family history was noncontributory.

The right eye was normal. Both the palpebral and the bulbar conjunctiva of the left eye were injected, and there was a frank yellowish, thick mucous discharge. Examination with the slit lamp revealed no evidence of active disease in either eye. The fundi were normal.

left eye a diffuse, hazy, nebulous opacity was located in the deeper third of the cornea and involved the lower half of the corneal area. The iris was atrophic; ring synechias were connected with flaky, fibrous veils that covered the pupillary opening. This pupillary material was crossed by numerous fine blood vessels. The left lens was densely cataractous. The intraocular tension (Schiøtz) was normal.

No reaction was obtained with 1.0 cc. of undiluted old tuberculin. The tonsils, removed in 1936, showed only chronic follicular tonsillitis, without evidence of tuberculosis or sarcoidosis.

The sequence of events during the course of the pulmonary disease was remarkable. The chest appeared normal in March and October 1936. In April 1937 bilateral increased density of hilar glands and bronchovascular markings had developed. In May 1937 the enlarged lymph nodes in the hilar region suggested Hodgkin's disease. In February 1938 the hilar lymph nodes regressed in size and the lungs became clear. By March 1941 the chest again appeared normal, and roentgenograms of the bones of the hands and feet at that time showed no abnormalities. The results of routine laboratory tests were normal, and intra-dermal tests gave no reactions. In 1939 the spleen and the superficial lymph nodes, except for the cervical nodes, became enlarged. An inguinal node removed at another hospital, showed a tuberculous structure. Examiners of the same slide at this clinic stated the opinion that the section was suggestive of sarcoidosis.

*Diagnostic Criteria.*—This case was the only one in which keratitis and anterior uveitis preceded the pulmonary disease. It was also of interest that the chest, the findings in which were indicative of hilar sarcoid disease (as well as Hodgkin's disease) at one stage, returned to a normal appearance. The opinion was expressed by the roentgenologists that such complete clearing would have been impossible had the disease been either tuberculosis or Hodgkin's disease and, for that reason, was strongly indicative of sarcoidosis. The pulmonary disease and the negative cutaneous reaction to undiluted old tuberculin were of first importance in the diagnosis in this case. The nodular type of iritis was more significant than the seroplastic type. The keratitis was noteworthy. Biopsy of the lymph node resulted in controversial reports.

CASE 9.—M. G., a white man aged 35, a laborer, was first seen in the eye clinic in September 1944. He stated that his left eye had first become red six months previously but had never been painful. He had been treated by several physicians. Two weeks before, he experienced a sudden decrease in vision and pain in the right eye. He gave no history of illness, chronic cough, fever, weakness or loss of weight. His past and family histories were noncontributory.

There was pronounced loss of vision, visual acuity being 2/200 in the right eye and 1/400 in the left eye. Both eyes had a moderately intense mixed injection of the ball, which was mostly ciliary. The caruncles were injected and swollen. Both corneas presented the following picture: There was a horizontal, bandlike macula. The opacities involved the deeper two thirds of the stroma and extended over half the cornea. The opacity of the cornea was greater in the lower than in the upper half. The epithelium was smooth and did not stain with fluorescein. There was no vascular infiltration. Many mutton fat keratic precipitates were deposited on the endothelium.

The anterior chamber was deep. Each eye showed posterior synechias of ring-like distribution, with entropion iridis and some tendency to iris bombée. New vessels appeared on the surface of the iris, and the pupillary aperture was well

remained clear. The fundi showed no abnormalities. The intraocular tension (Schiotz) was normal. Bacteriologic investigation of the conjunctival discharge revealed a few Staph. aureus organisms. Routine laboratory tests gave normal results, and the reactions to intradermal tests were negative.

Stereoscopic roentgenograms of the chest showed multiple bilateral rounded hilar masses with a few faint, small masses in the upper lobe of the right lung. Roentgenograms of the hands and feet revealed no abnormality. Multiple cutaneous plaques and nodules, slightly elevated, were located on the medial surface of the arms, the buttocks and the posterior and anterior aspects of the thighs. These lesions had a magenta cast, with slight scaling. Biopsy of the skin showed Boeck's sarcoidosis (fig. 6). Intradermal injections of old tuberculin gave negative reactions through strengths of 1:1,000, but there was no opportunity to carry the tests further. Examination of the nose did not show pathologic changes; no biopsy specimen was taken. In spite of the extensive involvement of the anterior segments, vision remained 20/50 in the right eye and 20/30 in the left eye.

*Diagnostic Criteria.*—The patient had iritis followed by keratoconjunctivitis. Intradermal injection of old tuberculin in a dilution of 1:1,000 gave no reaction. There was no opportunity for tests in lower dilutions. Biopsy observations on the skin were accepted as being highly indicative of sarcoidosis, and the roentgenograms of the chest as being equally suggestive in the absence of clinical evidence of other disease. Taken alone, the roentgenograms suggested the possibility of Hodgkin's disease, but considered together with the ocular involvement, they were interpreted as showing sarcoidosis. If the reaction to tuberculin had been positive, the possibility of caseous hilar tuberculosis would have been considered.

CASE 8.—E. G., a white housewife aged 25, was first seen in the eye clinic in March 1936, with the complaint of blurred vision in the right eye of five months' duration; there was no history of other ocular disturbance. She had not had chronic cough, fever, periods of weakness or loss of weight. The past and family histories were noncontributory.

Examination of the right eye revealed a clear cornea but definite injection of the bulbar conjunctiva. Deposited on the corneal endothelium were numerous mutton fat keratic precipitates. The aqueous contained about 30 cells per small pinhole fields of the slit lamp. The iris was dull, muddy, greenish blue and nodular. One large nodule extended from the root of the iris almost to the pupillary border; it had a raised, rounded surface; a muddy, dull brownish-gray color, and new-formed, superficial vessels. Three small nodules were seen at the pupillary margin. There were numerous posterior synechias. Precipitates occurred on the anterior capsule of the lens. The fundus was normal.

In the left eye the cyclitis was less intense. The iris was a clearer blue and without nodules; the fundus was normal. Vision was 20/100 in the right eye and 20/15 in the left eye. Intraocular tension (Schiotz) was normal in each eye. The patient was seen frequently until May 1941, when vision was 20/40 in her right eye and was limited to perception of hand movements at 8 inches (240 cm.) in the left eye. In the right cornea a nebulous, opacity, 1 by 1.5 mm., involved the deeper third of the stroma at the vertex. The aqueous still showed a slightly increased ray, but the cells and keratic precipitates had disappeared. The iris presented numerous posterior synechias and many atrophic areas corresponding to the location of the former nodules. The new vessels of the iris persisted. A retinal area,  $\frac{1}{8}$  D. in diameter, at the macula was characterized by its light orange color and central clumping of pigment. In the

later there was slight lessening of the hilar density; the bones of the hands and feet were still normal. In October 1945 roentgenograms showed that there had been complete clearing of the lesions previously noted (fig. 8B). The chest appeared normal.

*Diagnostic Criteria.*—Clinical evidence of sarcoidosis consisted of two factors: histopathologic changes in the lymph nodes compatible with sarcoid disease, and, most important, a typical roentgenologic picture of dense hilar nodules with bilateral fanning out of the bronchial vascular markings. Later roentgenograms showed clearing of the chest to a normal appearance. The roentgenologists stated the belief that such clearing would be impossible in a case either of ordinary

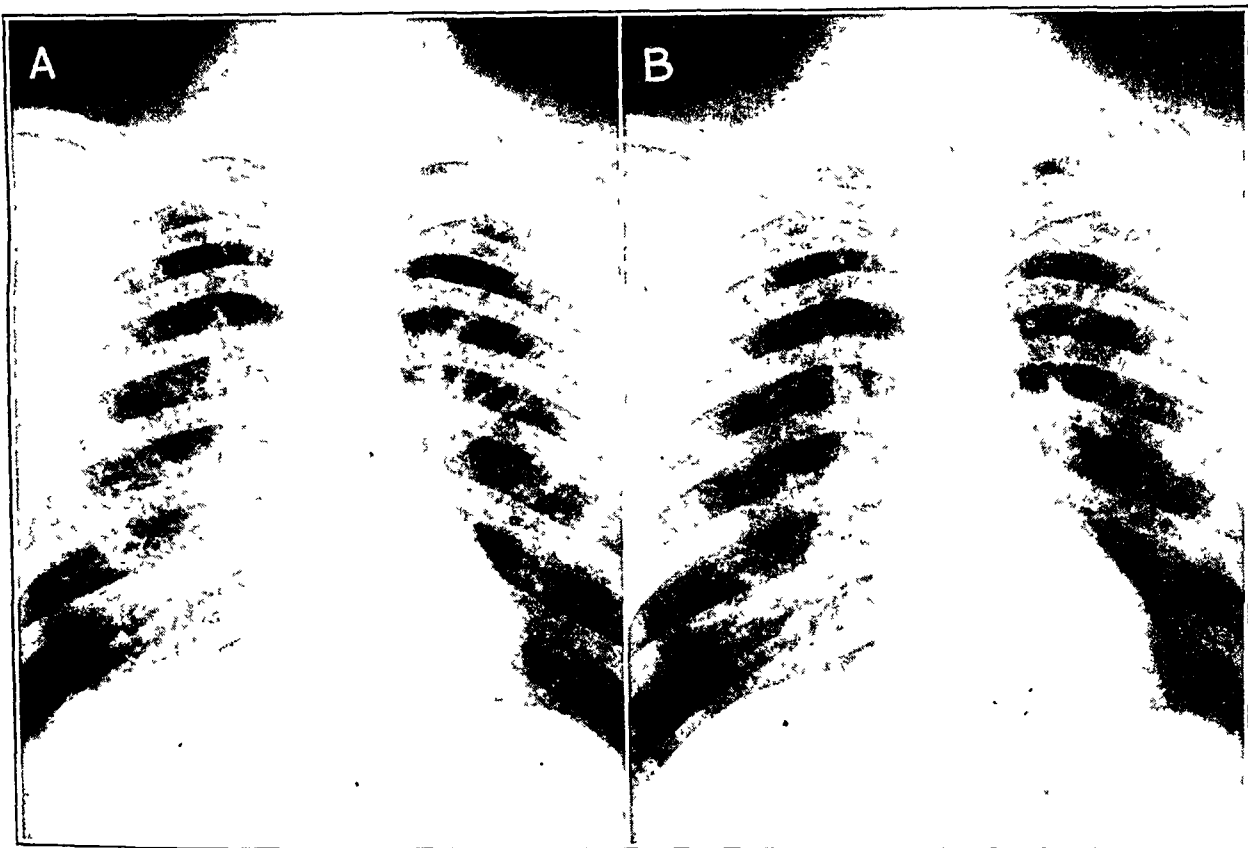


Fig. 8 (case 9).—A, roentgenogram of the chest (September 1944), showing marked hilar and parenchymal infiltrations, suggestive of Boeck's sarcoidosis; B, roentgenogram of the same chest as that shown in A, now with complete clearing and a normal appearance (October 1945).

tuberculosis or of Hodgkin's disease. The cutaneous sensitivity to tuberculin in dilutions of 1:100 was unexplained. The corneal opacities were the densest noted in any case reported here.

CASE 10.—A. W., a white housewife aged 42, was first seen in the eye clinic in March 1929. The patient stated that burning and itching of the right eye had begun three months previously and that one month later similar symptoms had developed in the left eye. There had been some tearing but no discharge. Vision was not affected at first, but later it was greatly decreased. There was no history of chronic or severe illness, chronic cough, fever, loss of weight or contact with tuberculous persons. The family history was noncontributory.



filled with a light gray membrane. A moderately mature, complicated cataract was present in each eye. Neither fundus could be visualized, but a good red reflex was obtained in each eye. The intraocular tension (Schiøtz) was normal in each eye.

The laboratory tests gave normal results, and the Kahn reaction was negative. Intradermal tests with old tuberculin gave positive reactions in dilutions up to 1:100 and negative reactions to greater dilutions. Other cutaneous tests gave negative reactions. Physical examination revealed enlargement of the superficial inguinal lymph nodes on both sides. There were no cutaneous lesions. Biopsy of an inguinal node showed markedly disrupted architecture (fig. 7). Throughout the node were areas of cells characterized by plentiful bluish to clear cytoplasm

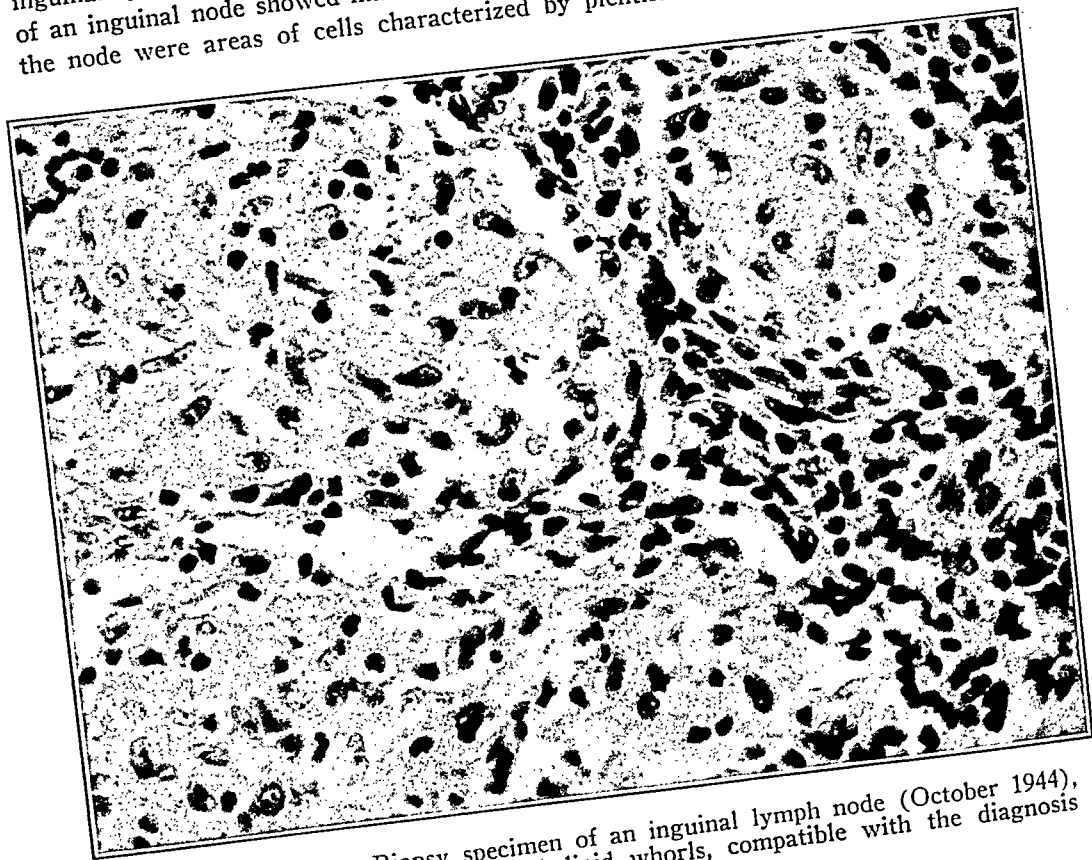


Fig. 7 (case 9).—Biopsy specimen of an inguinal lymph node (October 1944), showing multiple noncaseating epithelioid whorls, compatible with the diagnosis of Boeck's sarcoidosis;  $\times 460$ .

and one to three round, ovoid or sausage-shaped nuclei with light, fine chromatic stippling. The cells were arranged in swirls and masses, strongly resembling early tuberculoid formation. In large areas thick strands of collagenous substance twisted through them. No giant cells or areas of caseation or necrosis were seen. A few mitotic figures were present. The remaining lymphoid structure was normal. The impression was that of early tuberculosis of the lymph node or of possible Boeck's sarcoidosis. Stereoscopic roentgenograms of the chest were of special interest. In September 1944 roentgenograms showed dense bilateral hilar infiltrations which spread along the bronchovascular markings into each adjacent pulmonary field (fig. 8.4). The picture resembled that of pulmonary sarcoidosis. Roentgenograms of the bones of the hands and feet were normal. Six months

December 1939: Roentgenograms of bones of the hands and feet for the first time showed areas of rarefaction, with no evidence of sclerosis, in the triangular bones of the right wrist and anterior portion of the calcaneus and in the cuboid of the right foot. There were similar, but much less definite, areas of rarefaction in the navicular and lesser multangular bones of the left wrist. No changes in the phalanges of the hands were seen. These areas of rarefaction, without accompanying sclerosis of bone, are said to be characteristic of Schauermann's disease (sarcoidosis) and are usually found in the phalanges, rather than in the carpal and tarsal bones. A presumptive diagnosis of lesions of bone of Schauermann's disease was made.

October 1941: No change in lesions of the chest or bones.

In October 1947, the patient returned to the eye clinic, after an absence of six years. She appeared well and stated that she felt well and strong. Vision was 20/20 in the right eye and 20/30 in the left eye. In the right eye a central corneal nebula, 3 mm. in diameter, involved all layers, but chiefly Bowman's membrane. A highly refractile leukoma, 0.5 mm. in diameter, resembling a fatty infiltration, lay in the center of the nebula. The endothelium showed old deposits of pigment. Stahl's line below the opacity was well developed. Posterior synechias remained as thin, gray veils, and the pupillary opening was occluded; the iris was highly atrophic. In the left eye a highly refractile central corneal opacity, 0.5 mm. in diameter, involved the deeper epithelium and Bowman's membrane. Thin gray synechias continued as a veil over the pupil, and the iris was atrophic. The fundi were normal.

*Diagnostic Criteria.*—The patient had keratitis and nodular iritis. A series of roentgenograms of the chest over a period of eighteen years were diagnosed consistently as showing tuberculosis, even though the patient was sensitive to old tuberculin only in dilutions of 1:100. Lesions of bone, compatible in appearance with those of sarcoidosis, were observed in 1939, and at that time the diagnosis was changed to sarcoid disease. The fact that this woman had remained well in spite of the widespread pulmonary disease added credence to the diagnosis of Boeck's sarcoidosis.

#### COMMENT

The number of cases reported here is not large, and for that reason statistics must necessarily be inaccurate. Such a large series of as many cases of Boeck's sarcoidosis, with abundant ocular complications, is, however, infrequent in current ophthalmologic literature, and this report may add to present factual information.

*Frequency.*—Boeck's sarcoidosis appears to be a rare disease, but its exact incidence is not easily determined. In clinics of this university only about 30 cases are being followed with any degree of regularity, and this small number has been gleaned from over 450,000 registrations since 1927. The low incidence may be due to several factors: (1) This clinic is not a charity dispensary; (2) the social status of the patients seen is probably above the average, and (3) the percentage of Negro patients is small. It is also possible that there is some reticence among clinicians in making a diagnosis of Boeck's sarcoid. In 10 of the 30 cases of sarcoidosis collected from all clinic

Vision was 2/200 in the right eye and was limited to counting fingers at 4 feet (120 cm.) in the left eye. In the right eye, there was a heavy ciliary injection, and a central corneal opacity involved the anterior third of the cornea. The central leukoma faded to a macula toward the periphery. A superficial pannus extended over the limbus for 2 mm., without reaching the central opacity. The anterior chamber was of normal depth. Many mutton fat keratic precipitates, an increased aqueous ray and a few floating cells were seen. Posterior annular synechias were present, but there were sufficient openings to prevent the formation of iris bombée. The iris showed translucent, yellowish white nodules, 0.5 to 1.5 mm. in diameter, with vascularization about their bases. The pupillary aperture was filled with a cloudy, flocculent material. The fundus was normal.

The left eye presented a similar picture of central corneal opacity, aqueous cells, precipitates, synechias and cloudy material in the pupil. Intraocular tension (Schiotz) was normal. No tubercle bacilli were found after inoculations of guinea pigs with the aspirated contents of the anterior chamber of the right eye.

In 1936, after a stormy bilateral iritis, only a small central opacity in the anterior third of the cornea, with a definite Stahli line below, remained in each eye. The nodules of the iris disappeared, leaving marked atrophy. The pupils were fixed by annular synechias. The aqueous was clear. The moderate visual loss, with acuity of 20/30 in each eye, was caused by incipient complicated cataract. The fundi were normal. Routine laboratory tests revealed nothing significant and intradermal tests with old tuberculin gave reactions in dilutions of 1:100 and lower. A few macular lesions of the skin, diagnosed as tuberculids, developed on the face, arms and legs.

The sequence of events in the course of the pulmonary disease was unusual. A few of the many reports are summarized as follows:

March 1929: High grade tuberculosis of the hilar glands, particularly on the right side.

December 1929: Hilar tuberculosis; regression over a period of nine months ruled out the diagnosis of a malignant growth.

September 1930: Bilateral hilar tuberculosis, showing definite, but slight, parenchymal spread.

February 1931: Frank spread of tuberculosis into the parenchyma of the lung; fair degree of fibrosis and some calcification; advanced bilateral pulmonary tuberculosis of predominantly fibrous type, which had developed by spread from the hiluses.

June 1932: Slight increase in the fibroid type of tuberculosis; no notable changes from the February findings.

February 1933: An essentially unchanged appearance of advanced bilateral fibroid tuberculosis.

February 1934: Evidence of improvement in the upper lobe of the right lung; no change in the other pulmonary fields.

November 1935: Unchanged picture of bilateral pulmonary tuberculosis, predominantly fibrotic.

September 1936: Considerable emphysema; condition otherwise unchanged.

October 1936: Unchanged picture of atypical fibroid tuberculosis.

December 1937: Pneumonia superimposed on diffuse fibrous tuberculosis (pneumonia cleared uneventfully in a few weeks).

September 1939: No change in fibrotic lesions.

of previous anterior uveitis. In case 6 the left eye showed extensive pannus without evidence of anterior uveitis. There were extensive corneal opacities in case 7, and while the patient was under observation uveitis developed in the left eye.

Careful study of the histories and the earliest symptoms of ocular disease in these cases indicated that the sequence of events is probably that of an early conjunctivitis, followed by keratitis of varying degrees of severity, with the uveitis concurrent with, or not infrequently following, the conjunctivitis or keratitis. The idea cannot be entirely disregarded that the uveitis may be caused by corneal penetration by an unknown organism or toxic material.

Anterior Uveitis: Anterior uveitis existed in 9 of the 10 cases, In only 2 of these cases was it of the nodular type, whereas in 7 it was of the seroplastic type. In 2 cases the uveitis remained unilateral for nine months and two years, respectively, without evidence in the contralateral eye. In 7 of the 9 cases the uveitis became bilateral. Abundant keratic precipitates of the mutton fat type were characteristic of all cases of anterior uveitis. Heavy ring synechias were also present in all cases of uveitis, but in no case in this series did iris bombée actually develop. In several cases it seemed that such a complication would be inevitable, but at least one small channel between the posterior and the anterior chamber remained open. This feature appears to be characteristic of the iritis associated with sarcoidosis. Iridic atrophy was frequently observed in the later, quiescent stages. The nodular type of iritis, especially, seemed to lead to advanced atrophy of the iris.

Chorioretinitis: A chorioretinal lesion occurred in only one eye (case 8). Since this lesion was not proved to be active during the course of the general disease, it was only assumed that the ocular disease was due to sarcoidosis.

Complicated Cataract: Definite complicated cataract occurred in only 3 cases. In case 9 both eyes exhibited only moderate cataractous changes, and in case 8 one eye had a dense cataract. From these findings it would appear that, in spite of the severity of the anterior uveitis, complicated cataract is not frequent.

Tension: The intraocular tension, measured by the Schiøtz instrument, remained normal in all cases. In case 1 the tension of one eye mounted to 30 mm. of mercury, the highest reading obtained for any eye. It returned to normal limits within one week on cessation of instillation of atropine. The use of the atropine was then continued, without further rise.

patients in this university the eyes were involved. Eight of the 10 patients with ocular involvement were females. Five of the 10 were Negroes. Since Negro patients comprise about 1 per cent of the total daily number of patients who come to the clinics, it would appear that sarcoidosis is many times as frequent in the Negro race as in the white race, at least in this part of Chicago. The youngest patient was 25 years of age and the oldest 59; the average age was 36 years.

*Earliest Symptoms.*—Of the 10 cases, ocular symptoms were first noticed in 8, cutaneous lesions in 1 and symptoms referable to the chest in 1. The occasion for the first medical consultation corresponded exactly with the symptoms.

*Nonocular Disease.*—Pulmonary disease was present in all 10 cases; cutaneous lesions were noted in 6 cases; the lymph nodes were involved in 4, concurrent sinus disease was present in 3, and lesions of the bone were noted in 3.

*Ocular Symptoms.*—Lids: In 2 of the 10 cases there were extensive lesions of the lids. In case 4 both upper lids revealed intracutaneous papules. In case 5 lids showed brawny edema with subcutaneous nodules in the upper lids, accompanied with central notching and loss of cilia (fig. 5).

Conjunctiva and Cornea: These two tissues are discussed together because of the intimate relation of the symptoms and signs of conjunctivitis and keratitis found in 6 of the 10 cases. It is interesting to note that 7 of the 10 patients described their first symptoms as redness, itching and scratching. This is not significant in itself but assumes more importance when it is correlated with the earliest symptoms. In both cases 2 and 5 there was a heavy mucoid discharge, and in cases 4, 5, 6, 7, 8 and 9, conjunctival disease, which varied from intense hyperemia, swollen caruncles and follicles to conjunctival hemorrhages. Varying degrees of corneal involvement were also noted in cases 4, 5, 6, 7, 8, 9 and 10. Sclerosing keratitis occurred in case 4; corneal opacities, in cases 5, 7, 8 and 10; pannus, in case 6, and heavy band-shaped keratitis, in case 10. It might be argued that the corneal disease was only a complication of severe anterior uveitis. Such an opinion was given in the recent literature by other authors; however, the evidence presented here indicates that both the conjunctivitis and the keratitis are probably primary involvements, since corneal disease is not seen in 70 per cent of cases of heterogeneous anterior uveitis. Most important of all, in 3 cases there was definite corneal disease without evidence of past or present anterior uveitis. In case 4 there were a pannus and corneal opacities without evidence

contagious until proved otherwise. Radiation therapy has been tried both for the cutaneous lesions and for the hilar nodes of the lungs, without conclusive results. Calciferol (a pure crystalline form of vitamin D<sub>2</sub>) holds some promise of being beneficial. Dermatologists have used it in all their recent cases of sarcoidosis in doses of 50,000 international units of vitamin D three times a day, with promising results so far as the cutaneous lesions are concerned. A few patients suffered from nausea with this dose, but no other untoward results were noted. Calciferol was used in the last current case of iritis complicating sarcoidosis (case 2). Shortly after the use of calciferol, an extremely painful iritis became painless, and definite clearing of the aqueous began. From this single case, it cannot be stated whether the remission was coincidental or was due to the calciferol. Although cod liver oil was recommended for the treatment of lupus vulgaris in the latter part of the eighteenth century and solar therapy has long been advocated, it remained for Charpy,<sup>16</sup> in France, and Dowling and Thomas,<sup>17</sup> in England, to appreciate the probable effects of massive doses of vitamin D<sub>2</sub>. This work is considered by some to be the most important contribution to dermatology in recent years.

#### SUMMARY AND CONCLUSIONS

Boeck's sarcoidosis is discussed with regard to the many uncertainties in establishment of a clinical diagnosis. It has been demonstrated in the 10 cases reported here and in the writings of others that no single criterion or group of criteria exist to make possible a conclusive diagnosis of the disease. It is shown that experienced and well qualified specialists may disagree on the interpretation of the tissue biopsy and the gross appearance of lesions of the skin, eye or chest. Sarcoidosis is chiefly confused, usually on the basis of incomplete evidence, with tuberculosis, and less often with Hogkin's disease, syphilis, neoplasms, silicosis, leukemias, leprosy and other forms of lymphoblastoma.

Most important for a correct diagnosis of sarcoidosis are a good history of the disease; clinical evidence of diseases simulating sarcoidosis; low cutaneous sensitivity to intracutaneous injection of old tuberculin; biopsy of the skin; lesions of bone, as demonstrated in roentgenograms of the hands and feet; roentgenograms of the chest; biopsy of lymph nodes; gross appearance of cutaneous lesions; examination of the blood for albumin-globulin ratio, and ocular exami-

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16. Charpy, M. J.: Le traitement des tuberculoses cutanées par la vitamine D<sub>2</sub> à hautes doses, *Ann. de dermat. et syph.* 6:310-346, 1946.

17. Dowling, G. B., and Thomas, E. W. P.: Treatment of Lupus Vulgaris with Calciferol, *Lancet* 1:919-922 (June 22) 1946.

Vision: Visual acuities on last examination, with the approximate length of time each eye was known to be diseased, are tabulated for each case.

Case Number	Right Eye		Left Eye	
	Vision	Duration of Disease	Vision	Duration of Disease
1.....	20/16	1 yr.	Hand movements	1 yr.
2.....	20/100	1 yr.	20/25	Not involved
3.....	20/70	2 yr.	20/25	21 mo.
4.....	20/16	Not known	Light perception	3 yr.
5.....	Light perception	3 yr.	8/200	3 yr.
6.....	20/20	3 yr.	20/100	3 yr.
7.....	20/50	1 yr.	20/30	1 yr.
8.....	20/40	12 yr.	Hand movements	12 yr.
9.....	2/200	6 mo.	1/400	Few wk.
10.....	20/20	18 yr.	20/30	18 yr.

It was encouraging to note that if corneal opacifications did not develop the prognosis for reasonably good vision was excellent. If the eyes with keratitis and the eye with the large tumor are not included (cases 1, 4, 5, 6 and 8), the average vision for the involved eyes of this group was about 20/30, and no eye had vision of less than 20/100. One patient who had had severe bilateral uveitis for eighteen years retained 20/20 vision in the right eye and 20/30 vision in the left eye. The prognosis was not favorable for eyes with corneal involvement. These eyes had residual visions of light perception, 2/200, light perception, 8/200, hand movements and 1/400, respectively.

*Treatment of Ocular Complications.*—Since beneficial drugs had not been found, therapy was largely directed toward empiric treatment of the iritis. The chief aim was to prevent the formation of heavy synechias with a small pupil, which might result in filling of the pupillary aperture with organized exudates. In every case of iritis a 1 per cent solution of atropine sulfate was given several times a day. In no instance was the formation of posterior synechias prevented, even with a widely dilated pupil. It was found that the swelling of the iris was so great and the exudates so abundant that posterior ring synechias were formed, regardless of treatment. However, with this mydriasis, reasonably good pupillary opening was obtained in almost every case. Neither the atropine nor the disease produced secondary glaucoma.

*General Treatment.*—A modification of the regimen of rest for tuberculosis seemed to be in order. Nothing is known of the contagious aspect of the disease, but it should probably be considered

# OCULAR FINDINGS IN THREE HUNDRED AND TWENTY-THREE PATIENTS WITH SCHIZOPHRENIA

A Preliminary Report

MARTIN COHEN, M.D.

NEW YORK

THREE FACTS in connection with schizophrenia prompted this study: the prevalence and gravity of this mental ailment, the absence of recent ophthalmoscopic reports and the lack of micropathologic descriptions of the optic disk in cases of schizophrenia. New York state has twenty state hospitals for the mentally ill, with an average total population of 85,000 patients, of whom approximately 25 per cent are schizophrenic. Their treatment and care constitute an important medical, social and economic problem.

Although, in the past, there has been important research to determine the possible existence of pathologic changes in the nervous system and other organs in schizophrenia, little has been reported concerning the ophthalmologic findings. In general, studies of the fundus have not been considered in cases of mental disorders. Modern textbooks and other medical literature on psychiatry do not mention the ophthalmoscopic picture in schizophrenic patients.

In 1912, Tyson and Clark<sup>1</sup> included examinations of the fundus in their study of 115 cases of dementia precox at Manhattan State Hospital and found pallor of the optic disk in many. Since then, there have been no organized studies along these lines.

## PRESENT STUDY

*Material and Method.*—The group of 323 patients consisted of 243 men and 80 women, whose ages ranged from 18 to 77 years, most of them being in the younger and middle aged groups. The difference in the ocular conditions of the age groups will be discussed later. The patients were ambulatory and well nourished and presented the clinical manifestations of schizophrenia. The group represented the four types of schizophrenia: catatonic, 18 patients; paranoid, 249 patients; hebephrenic, 48 patients, and simple, 10 patients. The ocular findings did not differentiate one type from another. The patients were

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Read before the Section on Ophthalmology of the New York Academy of Medicine, March 15, 1948.

1. Tyson, H. H., and Clark, L. P.: The Eye Syndrome of Dementia Praecox. Arch. Ophth. 41:223-234, 1912.



nation, the items being listed in the approximate order of their reliability. It is of value to be able to detect more than one type of sarcoid lesion, but this advantage is equivocal in that, singly or in combination, the lesions do not necessarily establish a reliable basis for diagnosis. In the light of present knowledge, it is a matter of good judgment to be conservative in suggesting a diagnosis of sarcoidosis, for it is probable that many cases have been presented as instances of this disease with incomplete evidence. Each finding must be carefully evaluated as to whether it may strongly suggest, or only be compatible with the diagnosis of Boeck's sarcoidosis, and attention must be given to the question whether the experience and reputation of the reporting physician may justify a reliable opinion.

Ocular disease was present in approximately one third of the cases of sarcoidosis. The usual sequence of events for the ocular disease found in this series was the appearance of conjunctivitis, followed by some degree of keratitis, with anterior uveitis occurring with the conjunctivitis or keratitis, or following at a later period. Secondary glaucoma was not observed; complicated cataract was infrequent, and chorioretinitis was rare. The prognosis for good vision was excellent, even though the anterior uveitis was severe and active for many years. This, however, was true only in cases without corneal opacification.

Regardless of whether the physician wishes to think of sarcoidosis as a separate clinical entity or as a form of attenuated tuberculosis, from the standpoint of prognosis and possible differential treatment, the diagnosis of Boeck's sarcoidosis should be made whenever careful evaluation of the evidence may warrant a reasonably positive conclusion. Because the ophthalmologist is usually the first medical consultant, it is his obligation to recognize the possibility of sarcoidosis and to guide the patient to the necessary specialists for the confirmation or disproof of that diagnosis.

The University Clinics.

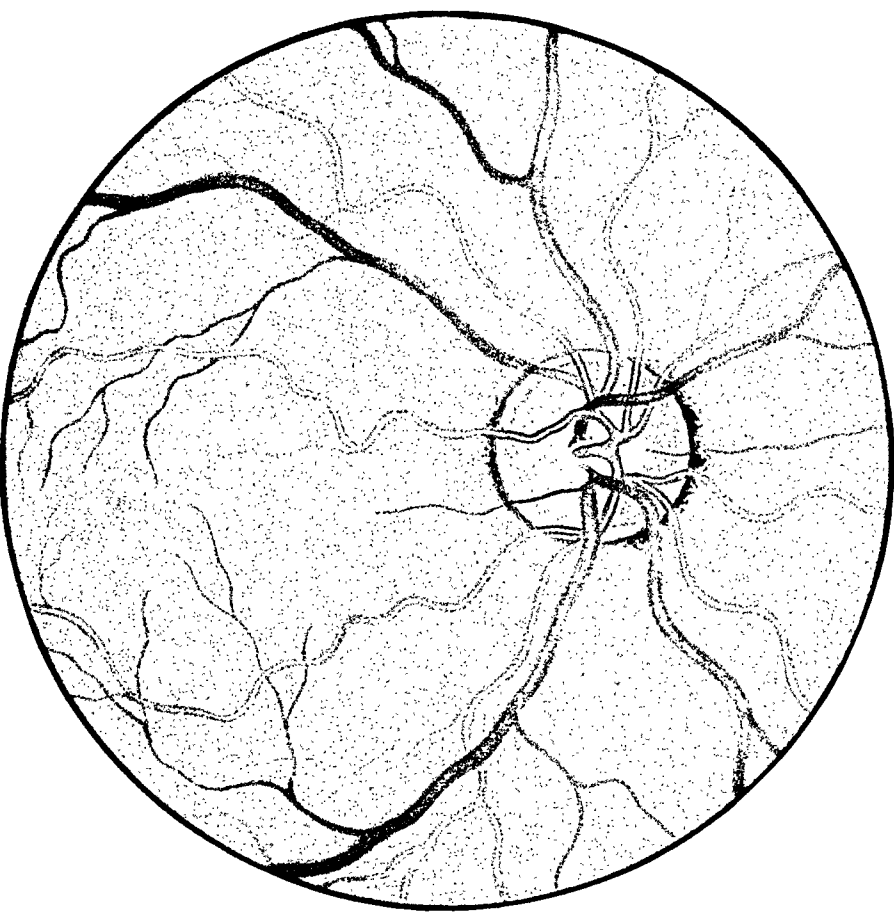


Fig. 1

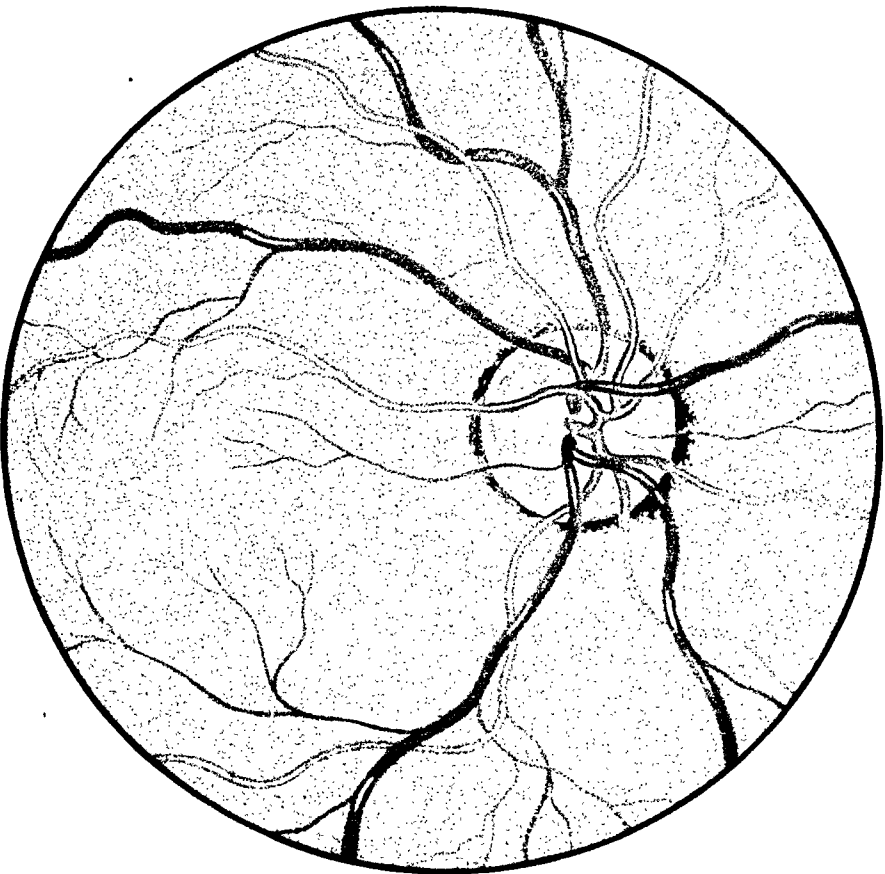


Fig. 2

Fig. 1. Marked Temporal Disc Discoloration.  
Fig. 2. Diffuse Disc Discoloration.

all free from systemic or infectious diseases, and none used alcohol or drugs to excess. Patients with any local ocular disease of primary or secondary origin or with myopia causing pallor of the disk were excluded.

A neuro-ophthalmologic examination was conducted on all patients with respect to ocular muscles; pupillary light reaction; gross visual fields, when possible; tension; exophthalmos; nystagmus, and ptosis. These tests were of negative value, as the findings and reactions were normal, particularly the pupillary responses. For the sake of continuity, I shall recall the pertinent anatomic facts.

Examinations of the fundus reveal the outgrowth of the brain tissue, namely, the optic nerve head and the retina, with its blood supply. The central retinal blood vessels and the capillary network on the surface of the optic nerve head or optic disk are in close anatomic connection with the cerebral and general circulation. The optic disk consists of nonmedullated nerve fibers, originating in the ganglion cells of the retina. These retinal nerve fibers continue their course through the visual pathway, that is, the optic disk, chiasm and optic tract, and terminate mainly in the external geniculate body, located in the mid-brain. From this junction, fresh nerve fibers, known as optic radiations, transmit the visual impulses to the ganglion cells in the cortex of the occipital lobe. Located in the center of the normal disk is the physiologic cup, consisting of perforations in the connective tissue membrane, the lamina cribrosa. The cup is brilliant white and at times is enlarged, so that the reflection from it may interfere with recognition of the normal color of the disk. On its inner side can be seen the nasal portion of the disk; on its outer side, the temporal portion. The border of the disk is sharply outlined. The normal color of the disk, as well recognized, is pinkish on its nasal portion, shading to a lighter pink on the temporal portion. This color varies with several factors, chiefly the intensity of the luminosity of the ophthalmoscope and the nature of the structure and vascularity of the disk. Variations in the normal color are well known and exist within physiologic limits. To judge whether variations are normal or abnormal requires experience and training in recognizing the variations in color of the disk in normal fundi. If the variation in color is normal, the results of the tests of visual acuity and visual fields will be normal. However, these tests are not applicable to schizophrenic patients, as the answers of these subjects are generally unreliable.

If a degenerative or inflammatory condition is present in the optic disk, this lesion, as seen with the ophthalmoscope, serves as a visible guide to diseases of the central nervous system, such as tabes, multiple sclerosis, alcohol poisoning and cerebral tumors. While engaged in this study of the eyegrounds in patients with schizophrenia, I noted especially a brown-gray color of the optic disk. Otherwise the fundus was normal. This color differed from the normal, as well as from the distinct gray or white of partial or complete optic nerve atrophy, as seen in cases of tabes or multiple sclerosis. This tawny gray color was, as a rule, present in both eyes, although in a few cases the disk of the right eye was more involved than that of the left. The reason for this difference could not be ascertained.

The cause of this discoloration could not be determined, as no neuropathologic examinations were available and no mention was found in the literature of any neuropathologic studies of the disk or retina in patients with schizophrenia. It cannot be stated at present whether this discoloration progresses, regresses or remains stationary; one will have to await the results of future investigations.

Thirty-four of the patients originally examined were intermittently reexamined over a period of six months; in 25 of these the condition of the disks seemed to have remained stationary, while in 9 the discoloration had become more pronounced. All the patients reexamined were under 40 years of age, and they were chosen for reexamination because all of them had shown either a temporal or a diffuse tawny gray discoloration of the disk.

The difficult task of selecting these 323 schizophrenic patients from the hospital wards was undertaken by Dr. Nobe E. Stein. Preparation for the examination consisted of instilling on the conjunctiva 2 drops of a 2 per cent solution of homatropine hydrobromide to facilitate observation of the fundus. Prior to examination of each group, I observed the fundi of several nurses with normal eyegrounds for the purpose of control and of testing the luminosity of the hand ophthalmoscope.

Patients were directed to look straight forward while the light from the ophthalmoscope was directed toward the optic disk in order that any difference in light or color reflections might be avoided. The light from the ophthalmoscope was of moderate intensity. A giantscope conducted on house current controlled by rheostat gives a more constant and more easily regulated illumina-

*Relation of Age to Color of the Optic Disk in Patients with Schizophrenia*

Appearance of Optic Disks	Number of Patients Examined in Various Age Groups (Years)				
	Under 30	30-39	40-49	50-59	Over 60
Total number of patients.....	37	48	86	89	63
Normal color.....	14	19	36	17	14
Strong temporal discoloration.....	16	12	21	24	11
Diffuse discoloration.....	7	17	29	48	38
Percentage of patients showing discoloration	61	60	58	81	78

tion than does the generally used hand ophthalmoscope. Unfortunately, the instrument was not available for this study.

Approximately 15 schizophrenic patients were examined each week for several months. The results of the examination were dictated for the records. Through the courtesy of Dr. John H. Travis, I was privileged to conduct this study at Manhattan State Hospital, beginning in May 1947.

*Results.*—In 100 patients (31 per cent) the color of the disks was normal; 84 (26 per cent) showed a pronounced brown-gray discoloration of the temporal portion of the disk (fig. 1), while in 139 (43 per cent) the discoloration was diffuse or complete (fig. 2). These findings indicate either a pronounced temporal or a diffuse discoloration in 223 patients (69 per cent). This is an unusually high incidence of abnormality of color. In the older patients, the brown-gray color might be attributed to vascular changes due to arteriosclerosis, but the retinal vasculature in these patients was normal. The percentage of young and middle-aged patients with discoloration of the disks must be considered excessive, since 102 of 171 patients under 50 years of age (60 per cent) showed this brown-gray color. Data on the relation of age to color of the disk are presented in the accompanying table.



## RESERVE ACCOMMODATION

HARRY EGGERS, M.D.

NEW YORK

**W**EAKNES of the accommodation is a frequent cause of asthenopia and should be tested for during refraction. There are various ways of doing this. I have devised a modification of the test for relative accommodation which I believe to be both rapid and reliable for clinical purposes.

### CAUSES OF ACCOMMODATIVE IMPAIRMENT

Accommodation may be difficult for several reasons. Three factors largely govern its ease of performance: the plasticity of the lens, the integrity of the innervation and the contractile power of the ciliary muscle.

Experience has shown that the full force of the ciliary muscle can be exerted for only a short interval without fatigue and resultant asthenopic symptoms. The increased contraction that is required in hypermetropia may be beyond the ability of the ciliary muscle to sustain for any length of time. In presbyopia the ciliary muscle does not seem to be lacking appreciably in actual contractile power, but the hardened lens substance resists the molding action of the elastic capsule and an increased muscular contraction is required to relax the restraining zonule sufficiently further to give increased molding force to the compressing capsule.<sup>1</sup> Since the organs of the human body do not age at a common rate, presbyopia may appear earlier than either the general appearance or the chronologic age of a person would suggest.

In diphtheria and botulism, toxins are believed to affect the cells of the Edinger-Westphal part of the oculomotor nucleus, or perhaps the cells in the ciliary ganglion. In syphilis, encephalitis lethargica and other infectious diseases, inflammatory lesions occur in or near the oculomotor nucleus. In the debility and avitaminosis of malnutrition or systemic disease, the fibers of the third nerve may be directly affected by degenerative changes which appear first in the myelin sheaths and later extend to the axis-cylinders. The ciliary muscle itself may be weakened whenever there is generalized muscular weak-

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1. I follow Fincham's theory of accommodation.

## COMMENT AND CONCLUSION

Since these observations on the fundus were personal, several ophthalmologists were requested to express their opinion regarding the changes in the optic disk. The majority of them confirmed the correctness of my observations.

Since the present study was concerned solely with schizophrenia, it is impossible to state whether changes in the optic disk are associated with other psychotic disorders. This phase of the subject will be reported on in a subsequent paper. The discoloration of the disk may be due to a degenerative, inflammatory, vascular, metabolic or toxic process affecting the optic nerve head. As previously stated, a neuropathologic examination of the disk in schizophrenic patients might serve to clarify the underlying cause of the discoloration.

In conclusion, the ophthalmologic manifestations and clinical findings suggest the probable existence of a pathologic process affecting the visual pathway in the brain of schizophrenic patients.

29 East Sixty-Fourth Street (21).

has more reserve accommodative power than an older person. This may be explained by the fact that a person with a more plastic lens requires a smaller contraction of his ciliary muscle during accommodation than does a person with a less plastic lens.

I perform my test in the following way: The subject's usual or proposed correction for distance is placed in the rear cells of the trial frame. Under good illumination, the subject is asked to read Jaeger 1 or Snellen 0.5 type aloud while holding it at exactly 11 inches (28 cm.) from the eyes. Equal minus spheres, usually from  $-1$  to  $-2$  D. in power, selected in inverse relation to the person's age, are simultaneously placed before each eye in the front cells of the trial frame. If the subject is able to continue his reading, the minus spheres are quickly replaced by others  $\frac{1}{2}$  D. stronger. Then, after a line or two more has been read, another quick increase of  $\frac{1}{2}$  D. is made. This is continued until finally the subject falters in his reading. The dioptric power of the minus spheres that were previously before the eyes— $\frac{1}{2}$  D. less than is being worn—indicates the amount of the reserve accommodation.

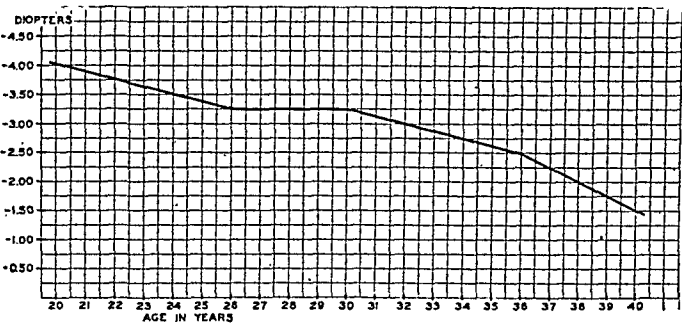
30 East Fortieth Street.



ness. Bacterial tonsillar or dental focal infection also weakens the accommodation. The *modus operandi* of such focal infection is not known.

MEASUREMENT OF THE RESERVE ACCOMMODATION

In order to determine the normal values, I measured the reserve accommodation of over 2,000 adults, who were about equally divided between the sexes. All these persons did at least three hours of fairly continuous reading or close work each day. The subjects were divided into two groups of approximately equal numbers—those with and those without symptoms of accommodative asthenopia. All persons with complaints that might be attributed to muscle imbalances or uncorrected astigmatism were excluded. For each group plottings were made on cross sectional paper, the ordinates representing diopters



Graph showing minimum normal additional accommodation, expressed in diopters, at a distance of 11 inches (28 cm.) for persons of various ages.

*Minimum Values for Reserve Accommodation at Distance of 11 Inches*

Age, Years	Reserve Accommodation, Diopters	Age, Years	Reserve Accommodation, Diopters
20	-4.00	32	-3.00
22	-3.75	34	-2.75
24	-3.50	36	-2.50
26	-3.25	38	-2.00
28	-3.25	40	-1.50
30	-3.25		

of reserve accommodations and the abscissas representing the subjects' ages.

It soon became apparent that a dividing line could be drawn between the plottings for the two groups. This is shown in the graph. A person whose reserve accommodation is less than the amount indicated needs a special correction for close work. The accompanying table presents the data on the relations shown graphically. No differences were found between the sexes. Normally, a younger person

directions of gaze and that these torsions can be shown by means of "after-images." Giraud-Teulon described it as follows.<sup>7</sup>

A linear after-image shows, after execution of a movement, the direction of the meridian which retained that linear image. . . . After-images are formed when, after the subject has fixated intensely a point for about twenty seconds, the gaze is turned toward a uniformly gray wall; then, after a few seconds, the after-image appears.

Ruete made these experiments with a bright red ribbon placed horizontally and then vertically, and also with two ribbons placed in the form of a cross, and observed the complementary green after-image. My colleagues and I made these experiments with an intensely luminous

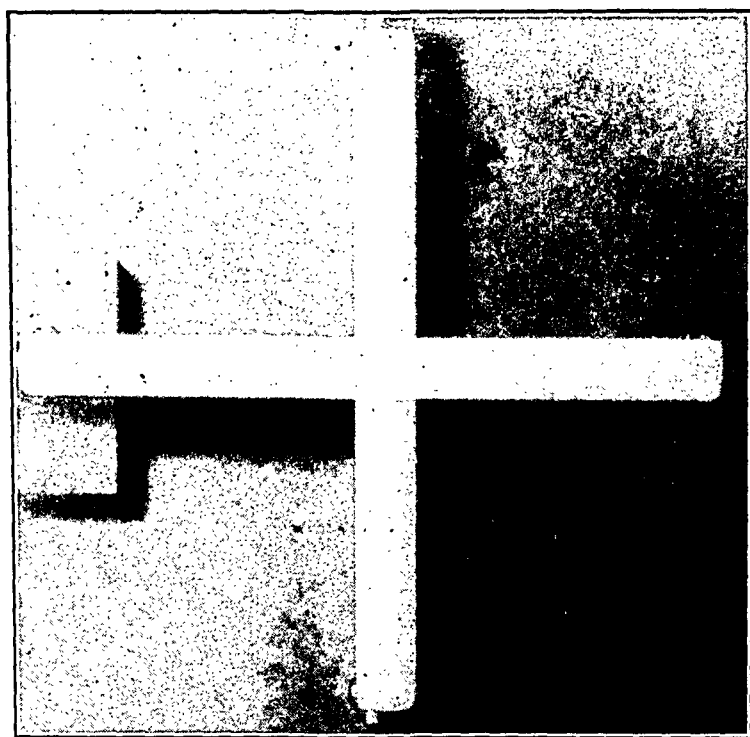


Fig. 1.—Luminous white cross (about one-half size).

white cross (fig. 1), observing a black cross as the after-image. To observe the phenomenon, the cross is placed in front and at the height of one eye or the other or of the two eyes at the same time. The results with each eye are almost always the same, but sometimes they are not, for reasons to be explained later. After the subject has intensely fixated on the center of the luminous cross the arms of which are vertical and horizontal, the light is extinguished and the gaze is turned on a vertical wall (without, however, moving the head), looking directly up or down, to the right or to the left, that is, along the directions of the two arms of the cross. The perpendicularity of the two arms of

7. Giraud-Teulon,<sup>3</sup> p. 649.

## SUPPOSED TORSION OF THE EYE AROUND THE VISUAL AXIS IN OBLIQUE DIRECTIONS OF GAZE

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THE ERRORS committed by great men are usually in direct proportion to their greatness. This has happened in the matter to be discussed here. From correct observations they have drawn wrong conclusions. I shall reconstruct this confused chapter in physiologic optics and ocular motility, using, in addition to the experiments of others, those of my own. This work had its origin in some questions about ocular torsion which were put to me by Dr. Joseph I. Pascal at our meeting in Mexico in August 1947. Frankly, I could not answer them satisfactorily, nor did we get much enlightenment when we consulted together the classic works of von Helmholtz,<sup>1</sup> Tscherning,<sup>2</sup> Giraud-Teulon,<sup>3</sup> and Le Conte,<sup>4</sup> the most recent works of Ives Le Grand,<sup>5</sup> and other publications. On parting, I promised Dr. Pascal to get to the bottom of this matter and the results of my investigations are presented in this paper.

The subject concerns facts and interpretations which the authors of books have copied from one another since the first experiments of Ruete<sup>6</sup> (1847). This body of observations was wrongly interpreted by Donders, and afterward by von Helmholtz, who affirmed that the eye undergoes torsional movements around the visual axis in oblique

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Presented before the Third Pan-American Congress of Ophthalmology, Habana, Cuba, Jan. 5, 1948 in condensed English translation.

The condensed translation was made from the Spanish by Dr. Joseph Pascal, to whom this paper is dedicated by the author.

1. Helmholtz, H.: *Optique physiologique*, translated by E. Javal and N. Klein, Paris, V. Masson & fils, 1887.

2. Tscherning, M.: *Optique physiologique: Dioptrique oculaire; fonctions de la rétine; les mouvements oculaires et la vision binoculaire*, Paris, G. Carré & C. Naud, 1898.

3. Giraud-Teulon, M. A. L. F.: *La vision et ses anomalies*, Paris, J.-B. Baillière & fils, 1881.

4. Le Conte, J.: *Sight*, New York, D. Appleton & Co., 1881.

5. Le Grand, I.: *Optique physiologique*, Paris, J.-B. Baillière et fils, 1946.

6. Ruete, C. G. T.: *Leerboek der ophthalmologie: In het Nederduitsch bewerkt met Aanteekeningen voorzien door Dr. Donders*, Utrecht, C. van der Post, Jr., 1847.

None of the three illustrious authors was right. It was Le Conte<sup>9</sup> who said, and Hering<sup>10</sup> agreed with him, that "the diagram [fig. 2A] is a correct representation of the phenomena seen in projection on a vertical plane, but it is not a representation of the torsion of the eyes." In order to eliminate the possible error due to the obliquity of the wall on which the image is projected, Le Conte arranged his experiments<sup>9</sup> (experiment 5) so that the after-image could be projected on a plane perpendicular to the visual line, i. e., on the inner surface of a large sphere at the center of which was the eye. In all these cases he found that the arms of the cross in the after-image were perpendicular to each other, though the cross as a whole was tilted in the same direction as the gaze (fig. 3). The tilt was greater, the greater the obliquity of the gaze. Le Conte arrived at the conclusion that the torsion of the eye was only apparent, since the movement was made

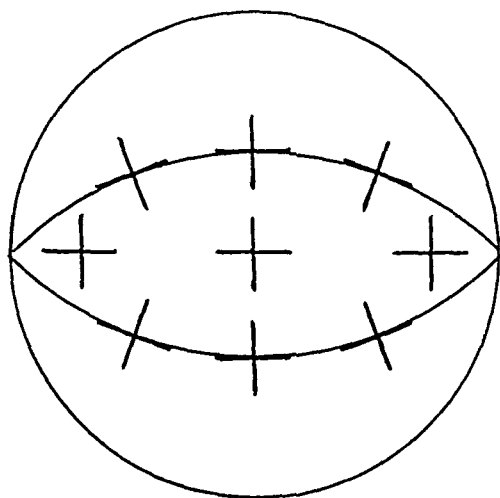


Fig. 3. (Tscherning<sup>2</sup>).—Experiment of Le Conte.

around an oblique axis situated in Listing's plane, or in the equatorial plane of the eye, and not around an anteroposterior axis, which is the characteristic of true torsion. It may be said in passing that true torsional movements do not normally take place for visual purposes and are made only as a compensatory rotation when the head is tilted, as I shall explain later.

Moreover, it is necessary, in discussing the previous experiments, to consider two reasons for the obliquity of the after-images, as pointed out by de Wecker and Landolt<sup>11</sup>: (1) the obliquity of the screen, mentioned before, and (2) a change in the inclination of the meridians of the eye. Although I have already referred to the influence of the

9. Le Conte,<sup>4</sup> p. 189.

10. Hering, E.: *Spatial Sense and Movements of the Eye*, Baltimore, Williams & Wilkins Company, 1942, p. 128.

11. de Wecker, L., and Landolt, E.: *Mouvements des yeux*, in *Traité complet d'ophtalmologie*, Paris, Vve. A. Delahaye et cie, 1885.

the cross in the after-image is preserved. But if the gaze is turned in intermediate directions, oblique to the two arms of the cross, the arms of the after-image no longer appear perpendicular to each other but form two acute angles and two obtuse angles. One acute angle is in the direction of the gaze, and the other acute angle is in the opposite direction; the obtuse angles are between (fig. 2*A*).

If, now, the luminous cross is turned so that its arms are oblique to the vertical and horizontal positions, the perpendicularity of the arms in the after-image remains when the gaze is turned obliquely along one or the other of the arms of the cross. But if the gaze is turned directly up or down, or right or left, the arms of the cross in the after-image are no longer perpendicular to each other but form acute and obtuse angles (fig. 2*B*). From these experiments, it was concluded (fig. 2*A*) that the vertical meridian was tilted in the same direction as the direction of gaze, for example, toward the right if the gaze was directed up and to the right. But it was not taken into

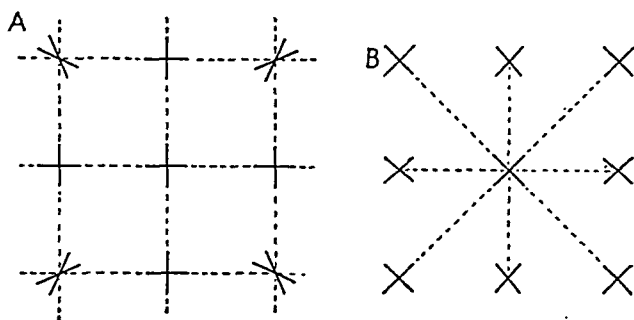


Fig. 2. (from Tscherning<sup>2</sup>).—The obliquity in the diagonal direction of gaze is greatly exaggerated.

account that the horizontal meridian showed exactly the opposite tilt, and that if attention were paid to its inclination the turning of the eye would have to be presented in the opposite direction. It is obvious, then, that both turnings could not take place at the same time if they were torsional movements around an anteroposterior axis of the eye. However, Donders and von Helmholtz interpreted them in this way, with the difference that Donders, concentrating on the supposed inclination of the vertical meridian, said that the inclination was in the same direction as the gaze, whereas von Helmholtz, thinking of the inclination of the horizontal meridian, stated that the torsion was in the opposite direction. This is a contradiction which the second of these illustrious men persistently and politely ignored, while seeking impossible conciliatory explanations. Giraud-Teulon<sup>8</sup> frankly acknowledged the contradictions, himself inclining to the opinion of Donders.

8. Giraud-Teulon,<sup>3</sup> pp. 669 and 672.

axes in the direction of movement, as in the previous case, there disappeared the perpendicularity of the arms of the cross; the arms then formed acute angles in exactly the same direction and did not coincide with the directions of the axes of the ellipse (fig. 4). Thus is shown the influence of the obliquity of the screen on the obliquity of the two arms of the cross, though in the case in which the light was moved in the direction of the arms of the cross, the perpendicularity of the arms was preserved. On the other hand, when the screen was perpendicular (as in projection on the surface of a sphere from its center), the perpendicularity of the arms of the projected image was preserved even when the cross as a whole was tilted, the two arms of the after-image having been rotated in the same direction as the gaze—toward the right, in the case discussed.

The second reason for the tilting of the arms in the after-image is an effective change in the inclination of the meridians and the axes

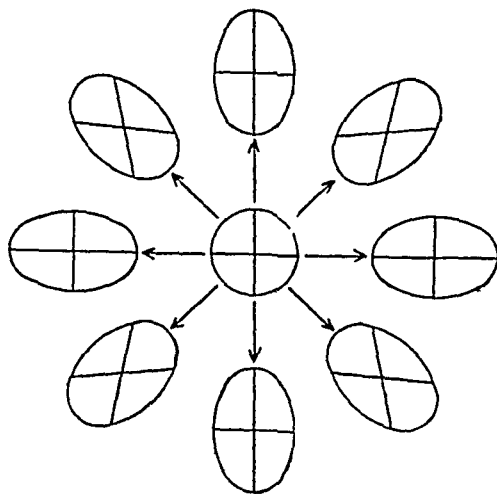


Fig. 4.—Elongation of circle to ellipse and obliquity of arms of cross.

of the eye. I refer now to the vertical and the horizontal; but, as Le Grand<sup>15</sup> pointed out, "one must not attribute to the vertical and horizontal directions special properties, since the law of Listing considers the primary position as an axis of revolution around which no direction is privileged. It is clear that this statement refers only to the mechanism of the ocular movements, since, from another point of view, that is, the division of the retina into two zones by the vertical meridian (the nasal in relation to the crossed fibers of the chiasm and the temporal in relation to the uncrossed fibers) the vertical meridian of the retina has a special significance, as will be shown later. The retinal image of the luminous cross remains always with its arms at right angles, although in certain oblique projections they appear otherwise.

15. Le Grand,<sup>5</sup> p. 173.

obliquity of the screen on which the image is projected, I must supplement this statement. Le Grand<sup>12</sup> wrote:

. . . the deformation of the cross can be explained by the simple effect of perspective, as a result of which a right angle is not projected as such on a plane unless at least one of its sides is parallel to that plane.

Tscherning<sup>13</sup> stated the same opinion, except that his concept was incomplete. He attributed the obliquity of the horizontal arm "to the projection of the after-image to a plane which was not perpendicular to the visual line," but he did not apply the same reasoning to the inclination of the vertical arm, which is in a similar condition. He limited himself to opposing, and with good reason, the opinion expressed by Donders and von Helmholtz, who attributed the obliquity to a "wheel-like" rotation around the visual line, and he pointed out that "such a rotation could not take place, since the axis in Listing's plane is perpendicular to the visual line." Le Conte<sup>14</sup> expressed the same opinion by saying that "there is merely an apparent rotation around the visual axis."

#### PRESENT INVESTIGATION

In order to settle this point regarding the perpendicularity or obliquity of the two arms of the cross in the after-image in relation to the obliquity of the screen, I carried out the following experiment: On the surface of the lens of an ordinary flashlight, a cross was drawn surrounded by a circle, and the shadow of this cross was thrown on a wall in a perpendicular direction, imitating that which takes place in the primary position of the eyes. The "shadow" image appeared as a cross with the arms perpendicular to each other, surrounded by a circle.

If, then, with the arms of the cross placed in a vertical and a horizontal position, the light was projected upward or downward along the direction of the vertical limb, the arms of the cross remained vertical and horizontal, but (and this has never been mentioned before) the vertical arm was longer than the horizontal arm and both appeared to be surrounded by an ellipse the major axis of which was vertical. If the light was turned in the direction of the horizontal arm, the ellipse appeared with its major axis horizontal. In either case the more oblique the projection on the wall, the more the ellipse was elongated in the direction of movement of the light. If, then, the light was projected, not along the direction of the arms of the cross, but in the intermediate directions, in addition to the formation of ellipses with the longer

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12. Le Grand,<sup>5</sup> p. 172.

13. Tscherning,<sup>2</sup> p. 276.

14. Le Conte,<sup>4</sup> p. 197.

that is, in the opposite direction). In the following discussion, I shall refer only to the upper extremity; when this is turned inward there is intorsion, and when this is turned outward there is extorsion. The horizontal axis is tilted so that its inner extremity is directed forward, upward and outward, its outer extremity turning in the opposite direction. The upper extremity of the vertical axis and the inner extremity of the horizontal axis move apparently in opposite directions (fig. 6), as a result of which, when the sphere is projected on the vertical wall laid out in squares, these come closer together and form an acute angle open upward and inward, or in the direction opposite the side toward which the gaze is directed.

2. On the anterior hemisphere, the vertical and horizontal meridians always make a right angle, and, seen from in front, they are tilted when the eye is turned on an oblique axis in Listing's plane, so that,

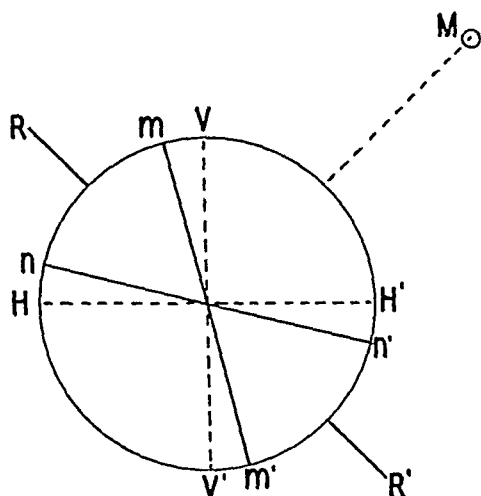


Fig. 6.—Apparent movement of the vertical and horizontal axes of the eye in opposite directions.

in the present example, the upper extremity of the vertical axis is turned inward and the inner extremity of the horizontal axis moves downward, with the result that in both there is an apparent movement of intorsion in a direction opposite the side to which the gaze is directed (fig. 7A).

3. On the posterior hemisphere, the vertical and horizontal meridians of the retina seen from behind, and always forming a right angle, are tilted so that the upper extremity of the vertical meridian is turned outward and the inner extremity of the horizontal meridian upward, with the result that there is apparent extorsion in the direction of the gaze (fig. 7B).

It is now apparent (1) that the vertical and horizontal axes move in opposite directions, and (2) that the vertical and horizontal meridians move in the same direction with reference to each other in each



In order to understand exactly what occurs with the different axes and meridians of the eye, one may take a sphere on which is drawn a vertical and a horizontal meridian, and on which is also indicated the vertical, horizontal and anteroposterior axes, and on the ends of the anteroposterior axis one may mark two circles, one in the center of the anterior half, to represent the cornea, or the pupil if you wish, and the other at the center of the posterior half, to represent the fovea centralis. One may pierce the sphere with long needles, which project a few centimeters beyond the sphere and which represent the aforementioned axes. At the level of the equator, or Listing's plane, are indicated between the vertical and horizontal axes two oblique intermediate axes. One may pierce the sphere with two needles in order to rotate the globe around the oblique axes in representing oblique directions of the gaze. Such an "eye" is placed between a vertical

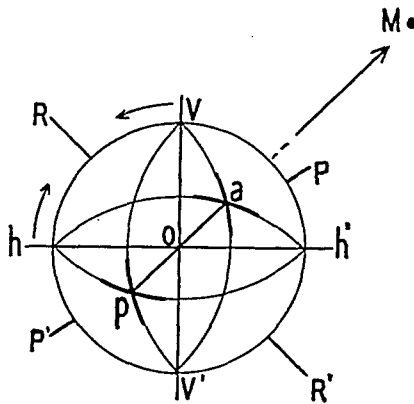


Fig. 5.—Axes of the eye and the vertical and horizontal meridians of the anterior segment (*a*) and of the posterior segment (*p*).

wall marked off in squares and the observer, and the experiment is begun.

Suppose one wishes to see what happens when the right eye turns up and to the right. The sphere having been placed so that its horizontal axis coincides with one of the horizontal lines and its vertical axis with one of the vertical lines of the "square," it is rotated around one of the oblique axes, the one which in Listing's plane goes from above and inward, down and outward.

1. First I wish to make a distinction, which I have not seen in any of the treatises, between what takes place with the vertical and horizontal axes of the eye which pass through its center of rotation, and what takes place with the vertical and horizontal meridians on the anterior and on the posterior hemisphere (fig. 5), that is, the retina. The upper extremity of the vertical axis is tilted inward, backward and downward (the lower extremity is tilted outward, forward and upward,

oblique axes, perpendicular to the direction of movement. These give rise to the tilting of the vertical and horizontal axes, which were erroneously interpreted as torsions by Donders, von Helmholtz and all those who followed them.

On the other hand, Le Conte,<sup>14</sup> Tscherning,<sup>16</sup> Maddox<sup>17</sup> and Hering<sup>10</sup> did not consider these as torsional movements. It is true that Hering made the error of considering the various inclinations of the vertical and horizontal axes, which are certainly opposite those seen in the projection of the after-images on a vertical wall (i. e., like that in figure 5 and opposite that in figure 2*A*). In order to explain the inclinations as they are really manifest, he was obliged to propose a completely arbitrary hypothesis<sup>18</sup> which it is not worth the trouble to reproduce or to oppose, notwithstanding my admiration for the eminent German master. Starting from a false premise, Hering confused the inclination of the axes, to which he referred and which have nothing to do with the obliquity of the after-image, with those of the meridians of the retina, which are really responsible for the obliquity of the image.

My views on ocular motility throughout my work on the subject<sup>19</sup> have always been opposed to the existence of true torsion, because, while it is certain that in such a movement the vertical axis is tilted inward or outward, the opposite is not true, since in every movement which does not take place around the vertical axis the axis must be tilted, without this showing that there was any torsion. I designate these inclinations produced on oblique direction of the gaze as pseudo-torsion.

Nevertheless, I must add two points: 1. The inclination of the after-images is usually slight (it has already been noted that the inclination has been much exaggerated in the figures (fig. 2*A* and *B*), and (2) the inclination varies with different observers and even at times in the two eyes of the same observer, and it may be zero in some cases. These variations are due to the existence in about 25 per cent of cases to a cyclophoria (ex-cyclophoria or in-cyclophoria), according to Savage (cited by Maddox<sup>20</sup>). This can produce a variation in the inclination of the after-image, increasing or decreasing it.

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16. Tscherning,<sup>2</sup> p. 272.

17. Maddox, E.: *Tests and Studies of the Ocular Muscles*, Philadelphia, P. Blakiston's Son & Co., 1907, pp. 43-45.

18. Hering,<sup>10</sup> p. 124, fig. 46.

19. Márquez, M.: (a) Un nuevo esquema didáctico sobre la acción de los músculos oculares extrínsecos, *Rev. de med. y cirug. práct.* **76**:49-60, 1907; (b) *Lecciones de oftalmología clínica*, Madrid, 1914, vol. 2, p. 345; (c) *Lecciones de oftalmología clínica especial*, Madrid, 1936, p. 241.

20. Maddox,<sup>17</sup> p. 236.

hemisphere and, moreover, that those on the anterior hemisphere move in the direction opposite those on the posterior hemisphere.

Another interesting fact has not previously been mentioned. Whereas in movements around axes in Listing's plane the anterior hemisphere moves in a direction opposite the posterior hemisphere, in rotatory movements around an anteroposterior axis the anterior and posterior hemispheres move in the same direction, so that, for example, the upper vertical radius of the cornea or of the iris moves in the same direction as the upper vertical radius of the retina. It is important that one remember this in order to understand the projection of the after-images.

I insist that the movements produced in oblique directions of gaze are not torsion movements, as Donders and von Helmholtz maintained, but are movements of pseudotorsion. True torsion movements (wheel-like rotations) do not normally take place as movements for visual purposes.

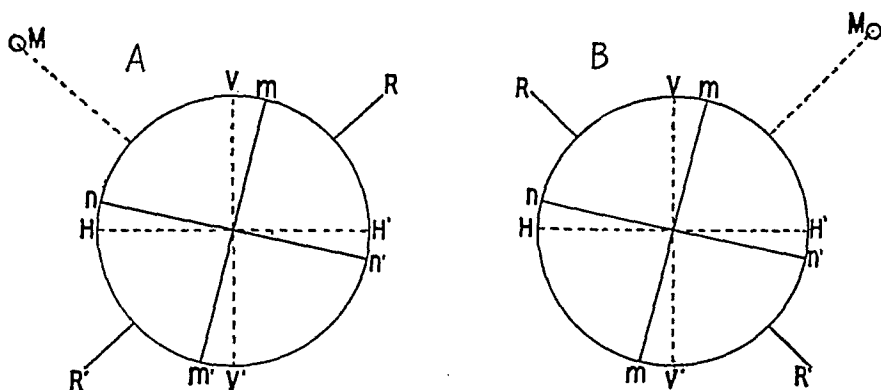


Fig. 7.—*A*, rotation of the meridians of the anterior segment, opposite the direction of gaze. *B*, rotation of the meridians of the posterior hemisphere in the direction of gaze.

Vision, it has been well said, is like touching at distance with the fovea (which is at the ocular end of the visual axis). If the visual line is already in the direction of the point of fixation, torsional movements are unnecessary; and if it is not, torsional movements will not place it there and are therefore useless. However, its usefulness for compensatory movements is undeniable, as will be seen later.

On the other hand, in all movements for visual purposes, whose axes of rotation are in Listing's plane, the fovea, being farthest from the axis of rotation, can be moved with the least muscular force. Movements of this type are produced (1) around a vertical axis—adduction and abduction, in which movements the axis does not change place; (2) around a transverse horizontal axis—elevation and depression, in which the vertical axis moves in an anteroposterior direction, describing a circumference by its upper extremity, and (3) around

added to that of the external rectus, as in the case of the inferior oblique, and an intorsion effect which is considerably increased in looking up and out, according to the calculations made on my (muscle) scheme by Dr. Rivas Cherif,<sup>22</sup> which action would oppose extorsion of the vertical meridian.

I stated in 1907<sup>19a</sup> that the so-called torsion movements of the eyes on tilting the head to either shoulder, which according to Tscherning cannot be fully compensatory, since they do not exceed 6 or 7 degrees, are made for the purpose of having the impressions from the right side always fall on the two left halves, and those from the left side fall on the two right halves, of the retinas. Without these small

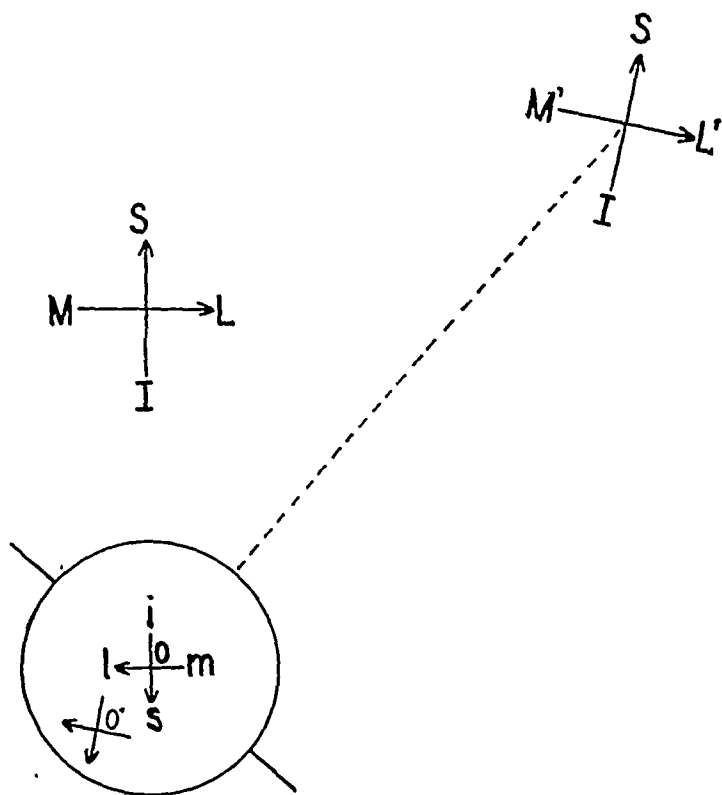


Fig. 8.—Explanation of the formation of the after-image in an oblique direction of gaze (Márquez).

compensatory movements, the inclination of the head to one side or the other would result in the impression sometimes being transmitted by the uncrossed fiber bundle and at other times by the crossed fiber bundle of the chiasm. This would produce the greatest confusion in the visual centers. This observation of mine, which passed unnoticed, was revived in 1927 (twenty years later) by Tschermak,<sup>23</sup> who stated

22. Rivas Cherif: Oral communication to the author, 1946.

23. Tschermak, A.: Ueber die funktionelle Bedeutung der Sechszahl der Muskeln des Auges, *Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch.* **46**:5-14, 1927.

The influence of false torsion on the inclination of the image is exactly opposite that of true torsion (cyclophoria). In cyclophoria and in cyclotropia the false image is projected in a direction opposite the rotation of the eye, as is true of the false image in all cases of muscular imbalance. In false torsion the true image, on being projected as an after-image, is inclined in the same direction as the rotation of the eye, since it is the result of the first impression on the meridians of the fovea.

The reason for the inclination of the after-image will be readily understood from figure 8, in which I shall prove that, in addition to the fovea being displaced in this case downward and to the left, its vertical and horizontal meridians have been tilted in the same direction as that of gaze. This does not conflict with the observation that the projected image is inverted up and down and to the right and the left with reference to the retinal image. This explanation in terms of geometric optics, which, incidentally, coincides with that of Dr. Joseph Pascal (personal communication), is completely satisfactory, something which cannot be said of the explanation (in terms of physiologic optics) of Hering or, finally, that of pathologic optics, in which this case of the obliquity of the retinal meridians is compared with what occurs in cyclophoria. I have already indicated the differences between the false image in cyclophoria and the true after-image, and the variability in the inclination of the after-image due to the interplay of these two factors.

In reality, these movements of pseudotorsion are slight and result from the fact that the vertical meridian in not turning around an anteroposterior axis of rotation must necessarily be inclined when the eye turns around an oblique axis.

On the other hand, there is a natural tendency in the eye to maintain the verticality of the vertical meridian. As a result, there are compensatory rotatory movements of the eyes when the head is inclined to either shoulder, as was pointed out by Nagel and others. When the eye looks up and to the right, the muscles involved are the superior rectus and the right inferior oblique, which in extreme abduction has completely lost its elevating action (according to the calculations of van der Hoeve<sup>21</sup>), but its two other actions are at a maximum, i. e., the abduction which is added to that of the external rectus and the extorsion. This would produce a marked extorsion did not the superior oblique come into play in order to prevent the vertical meridian from losing its verticality. This muscle has no depressing effect on the eye in abduction, but it has an abduction effect, which is

21. van der Hoeve, J.: Ueber Augenmuskelnwirkung und Schielen, *Klin. Monatsbl. f. Augenh.* 68:492, 1922; *Ocular Movements*, Bowman Lecture (1932), *Tr. Ophth. Soc. U. Kingdom* 52:1-31, 1932.

tion has practically no elevating effect but has a strong abduction and extorsion effect, the extorting effect being neutralized by the intorting effect of the superior oblique muscle.

I have shown that normally there are no torsion movements for the purpose of aiding vision and that those movements which appear as torsion are in reality pseudotorsions produced by rotation around an oblique axis in Listing's plane. Real torsional movements would be unnecessary if the visual axis was directed to the point of fixation and would be useless if the visual axis was not so directed, as such movements cannot place the eye in the proper direction.

There exist slight torsion movements which Tscherning estimated at a maximum of 6 to 7 degrees. These have nothing to do with the pseudotorsion produced in oblique directions of gaze. These slight torsion movements are for the purpose (Márquez,<sup>19a</sup> Tschermak<sup>23</sup>) of preserving the verticality of the vertical meridian of the retina in order to avoid the confusion which would result in the visual centers if visual impressions were sometimes transmitted by the nasal half of the retina and the crossed fibers of the chiasm and at other times by the temporal half of the retina and the uncrossed fibers of the chiasm.

37 West Ninety-Seventh Street, New York (25).

the opinion that these movements "were made in order to maintain the exact sensorial correspondence of the two retinas."

The fundamental error in the interpretation of the after-images in oblique directions of gaze has been twofold: on the one hand, that of attributing the inclination of these images to a torsion of the eye around the visual line, instead of to a pseudotorsion on an oblique axis in Listing's plane and, on the other hand, that of confusing the axes of the eye which pass through the center of rotation, and which play no part in these phenomena, with the vertical and horizontal meridians of the retina which pass through the center of the fovea, whose inclination in the same direction as that of the gaze determines the obliquity of the after-image by a mechanism purely of geometric optics.

#### SUMMARY

The experiment of Ruete about the middle of the last century showed that the after-image of a bright cross with vertical and horizontal arms when projected obliquely on a vertical wall lost the perpendicularity of its arms, which were then inclined at an acute angle. This observation was erroneously interpreted by Donders and by von Helmholtz as due to a movement of torsion or of rotation around the visual axis.

I consider this interpretation unfounded and have shown in various publications since 1907 that, whereas in cases of torsion of the eye the vertical axis is inclined toward one side or the other, the opposite is not necessarily true, since it can be inclined in other types of movement, namely, in rotations on an oblique axis in Listing's plane, such as happens in pseudorotation.

I have shown by means of new experiments the mechanism which produces the obliquity of the after-image. Le Conte showed that when the screen of projection is perpendicular to the line of gaze the arms of the cross remain perpendicular to each other, although the cross as a whole is tilted in the direction of the gaze. I have shown that this tilt has been much exaggerated by previous authors, that it varies from one observer to another and even for the two eyes of the same observer, and that it may be zero. One cause of error is the frequent occurrence of cyclophoria of a greater or less extent, which distorts the results of the experiment.

A study of the ocular movement shows the influence which they exert not only on the axes of the eye but also on the vertical and horizontal meridians at the anterior and posterior poles of the eye. A study of the meridians at the fovea and their inclination in the same direction as the direction of gaze explains the obliquity of the after-image. As an example of the muscles involved in any oblique movement, one may take that of looking up and to the right. The superior rectus is the maximum elevator muscle; the inferior oblique in abduc-

*Physical Examination.*—The patient was fairly well developed but poorly nourished. Inspection of his back revealed many soft, doughy masses along the course of the intercostal nerves (fig. 2). There were several small, soft mollusca fibrosa on the anterior abdominal wall. A number of café au lait patches were scattered over the trunk and thighs. Along the inner aspect of the



Fig. 1.—Excision of a neurofibroma involving the left ulnar nerve.

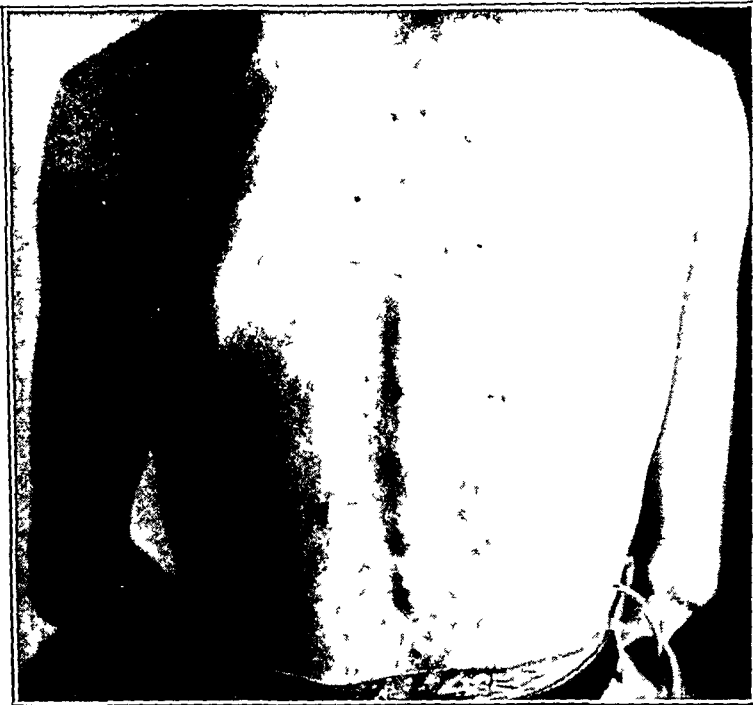


Fig. 2.—Neurofibromas along the course of the intercostal nerves on the posterior part of the body.

left arm distinct, soft masses ranging from 0.5 to 1.5 cm. in length (fig. 3), could be palpated. The blood pressure was 124 systolic and 72 diastolic. The liver and spleen were not palpable.

On March 26, red blood cells numbered 4,490,000, with 99 per cent hemoglobin. The white cell count was 6,150, with 58 per cent polymorphonuclear neutrophils, 36 per cent lymphocytes, 4 per cent monocytes and 2 per cent basophils. The Kahn reaction was negative. On April 25, the sedimentation rate



# NEUROFIBROMATOSIS ASSOCIATED WITH TUMORS OF THE OPTIC PAPILLA

Report of a Case

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NEW YORK

A NEUROFIBROMATOUS growth of the optic papilla is indeed rare. Up to the present, only 1 such case has been recorded in the literature (Stallard<sup>1</sup>). It is the purpose of this paper to report another case, in which both optic disks were similarly involved. The patient also manifested numerous other abnormalities which are associated with neurofibromatosis (von Recklinghausen's disease).

## REPORT OF CASE

*History.*—A white man aged 26, private first class in the Army of the United States, was admitted to a regional station hospital on Oct. 6, 1945, because of abdominal pain. There was a history of symptoms of duodenal ulcer for four or five years. A roentgenologic series of the gastrointestinal tract clearly showed a deformity of the duodenal cap. The patient was placed under strict dietary control, with complete relief from his annoying epigastric complaints.

It was also established at the time of his admission that for nine years he had had gradual loss of hearing, which audiometric and other hearing tests showed to be 54 per cent. He had had the usual diseases of childhood except scarlet fever and diphtheria. His mother, father and one brother were alive and well. There was no history of hereditary familial disease.

Examination of the anterior surface of the left forearm revealed a tumor of moderate size which was freely movable and was unattached to the underlying structures. The rest of the physical examination was incomplete.

On Dec. 19, 1945 the patient was transferred to the Borden General Hospital for a hearing aid. A surgical consultant diagnosed the tumor of the left forearm as a lipoma and advised its removal. On Jan. 19, 1946 the tumor was excised (fig. 1); it was found to be intimately attached to the ulnar nerve. The pathologic diagnosis, made on January 29, was perineurial fibroblastoma.

The question of mental deficiency was raised, since the patient had completed only the third grade in grammar school. This suspicion was confirmed by the Wechsler-Bellevue tests, which demonstrated an intelligence quotient of 74. The brother was also mentally deficient. On March 24, the patient was transferred to Moore General Hospital.

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Presented at a meeting of the New York Academy of Medicine, Section of Ophthalmology, April 19, 1948.

1. Stallard, H. B.: A Case of Intraocular Neuroma (von Recklinghausen's Disease) of the Left Optic Nerve Head, *Brit. J. Ophth.* 22:11, 1938.

was 18 mm. in one hour, and the hematocrit reading was 45. The urine gave a negative reaction for albumin and sugar, but microscopic examination revealed the presence of a few pus cells. Lumbar puncture on April 27 showed that the spinal fluid was normal and under normal pressure.

A roentgenogram, taken on April 25, demonstrated a round, homogeneous, soft extrapleural shadow extending into the apex of the right lung (fig. 4). The mass measured 3 by 4 cm. and was directed downward. The shadow had no connection with the ribs or other bony structures. Roentgenographic studies of the skull on this date showed no alteration from the normal. It was suggested that another specimen be taken for biopsy.

On May 17, a small, doughy mass was removed from the patient's back. Pathologic examination (Major B. Bornstein, chief of laboratory) was reported on May 27, as follows: The mass was soft, rubbery and ovoid, measuring 24 by 12 mm. The surface was smooth and covered on one side by a thin membrane. On cross section the mass was white and showed sago-like granulation. Microscopic examination revealed that the mass was composed of fibers arranged in broad strands and whorls, which contained long, spindle-shaped nuclei, the nuclei in places assuming a palisade appearance (fig. 5). The tumor was surrounded and traversed by strands of loose, collagenous connective tissue. Only a few small capillaries were seen in the connective tissue. The diagnosis was neurofibroma.

*Ophthalmologic Consultation* (May 4).—Vision was 20/200 in the right eye and 20/20 in the left eye, unimproved by correction. Refraction gave the following values: right eye: +0.50 D. sph.  $\ominus$  +0.50 D. cyl., ax. 180; left eye: +0.50 D. sph.  $\ominus$  +0.25 D. cyl., ax. 90. Movements of the extraocular muscles were full in all cardinal directions. Digital palpation showed that the intraocular pressure was within normal limits. There were no lesions of the eyelids or the conjunctiva. No ptosis or exophthalmos was noted. The right pupil was larger than the left and reacted sluggishly to light but well in accommodation. Horner's syndrome was not present. The cornea, lens and vitreous were clear.

*Fundi*: Right eye: A growth of newly formed tissue projected forward from the disk. Its surface was striated but appeared nodular in several areas. The disk was elevated 4 D. nasally and 5 D. temporally (fig. 6). The nasal half was a dull grayish red. No hemorrhages or exudates were visible on the summit or within the circumpapillary space of the elevated disk. The temporal half of the disk was whitish gray and was thrown into vertical corrugations, which proceeded superiorly 3 disk diameters and inferiorly 4 disk diameters, tapering into well defined striations in both directions. Each extremity assumed a forked appearance. The temporal sector of the disk simulated the color scheme seen on the nasal side. The new growth on the disk masked the appearance of the emerging vessels. The superior and inferior nasal veins were the only vessels visible on the summit of the tumor. The temporal vessels were first clearly seen at a distance of about 1 disk diameter from the raised papilla. The veins were full and nontortuous and did not present arteriovenous nicking. The retinal arteries gave an increased central light reflex and appeared somewhat attenuated, so that the ratio of arteries to veins was 1:2. Immediately superior and inferior to the disk, the fundus took on a tigroid appearance. A circumscribed, grayish white patch, measuring  $\frac{1}{2}$  disk diameter, was observed in the macular region, two pigment spots being located within its center. A similar, but smaller, patch was located in the inferior temporal quadrant. A small,



Fig. 3.—Inner aspect of the left arm revealing the small neurinomas of the cutaneous nerves.

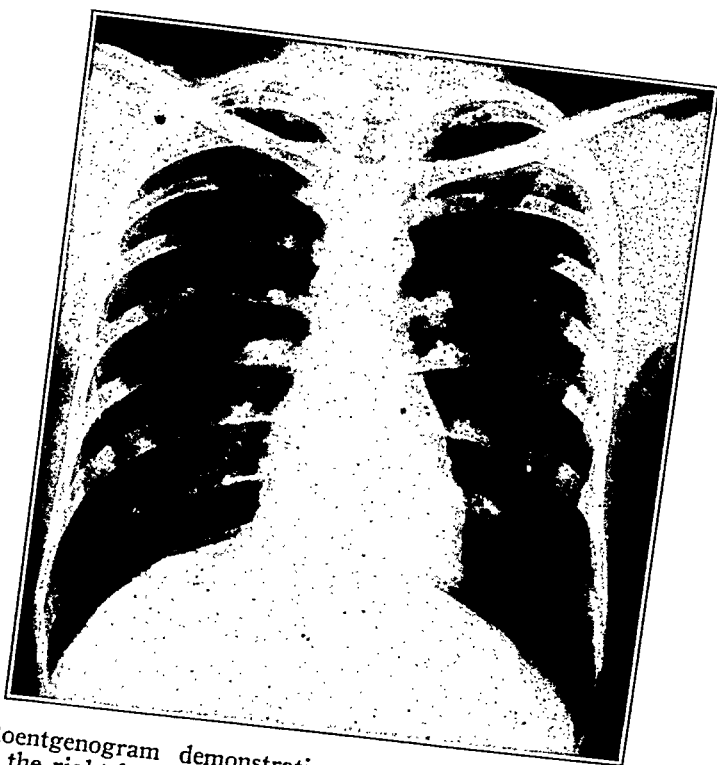


Fig. 4.—Roentgenogram demonstrating a homogeneous, circumscribed mass in the apex of the right lung.

yellowish, highly refractile body was observed below the macula and was in close relation to a fine terminal vein. In the 8 o'clock meridian, about 4 disk diameters away, was a collection of discrete, yellowish flecks. They varied in size and shape, the majority appearing oval. The rest of the periphery was within normal limits.

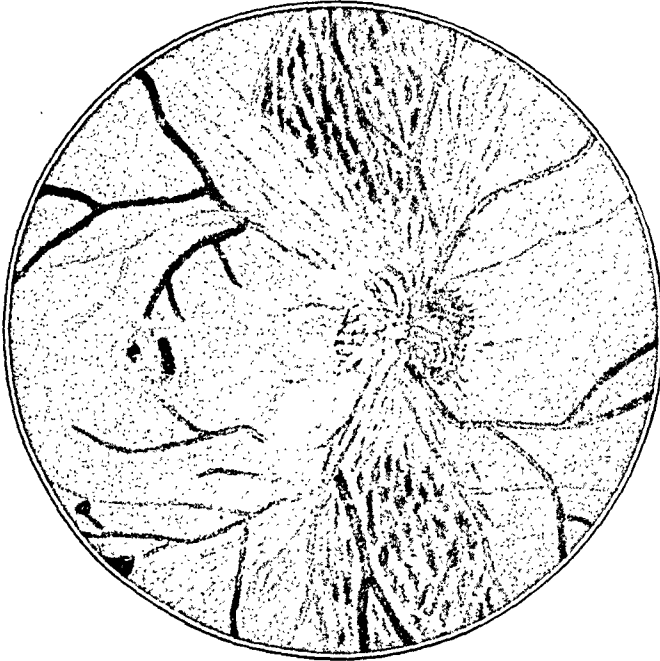


Fig. 6.—Fundus of the right eye, showing tumor of optic nerve head with retinal fiber medullation, central chorioretinitis and segmental choroidal sclerosis.

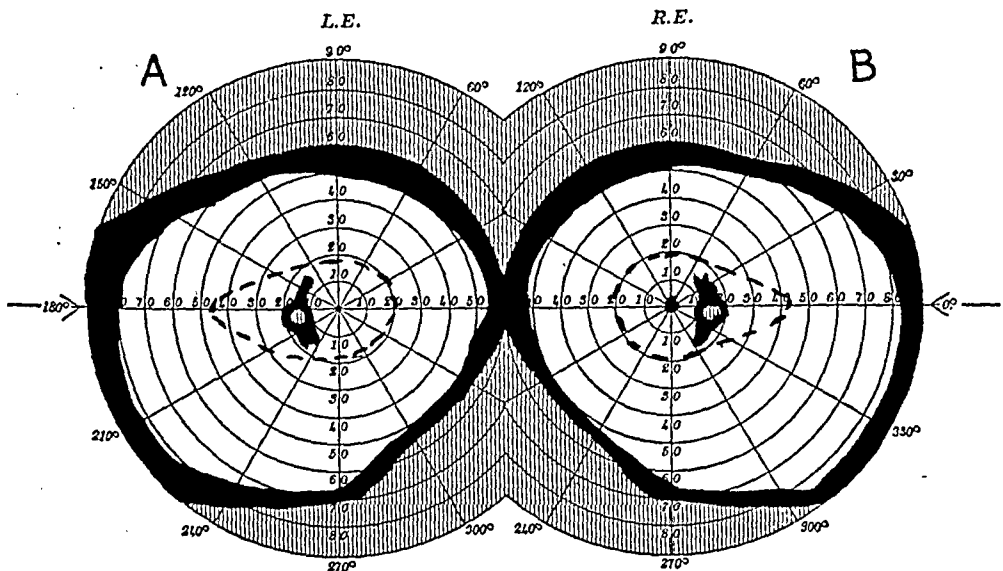


Fig. 7.—Visual fields on May 5, 1946.

*A* (left eye), enlargement of the blindspot, but smaller than that in the right eye (*B*), no central scotoma; vision 20/20 without correction. Fields were taken with 2 mm. white and 5 mm. red targets at 330 mm.; broken line shows field for red.

*B* (right eye), double comma enlargement of the blindspot with forking of extremities corresponding to medullation of the optic nerve; absolute central scotomas for red and white; vision 20/200, uncorrectible. Fields were taken with 2 mm. white and 5 mm. red targets at 330 mm.; broken line shows field for red.

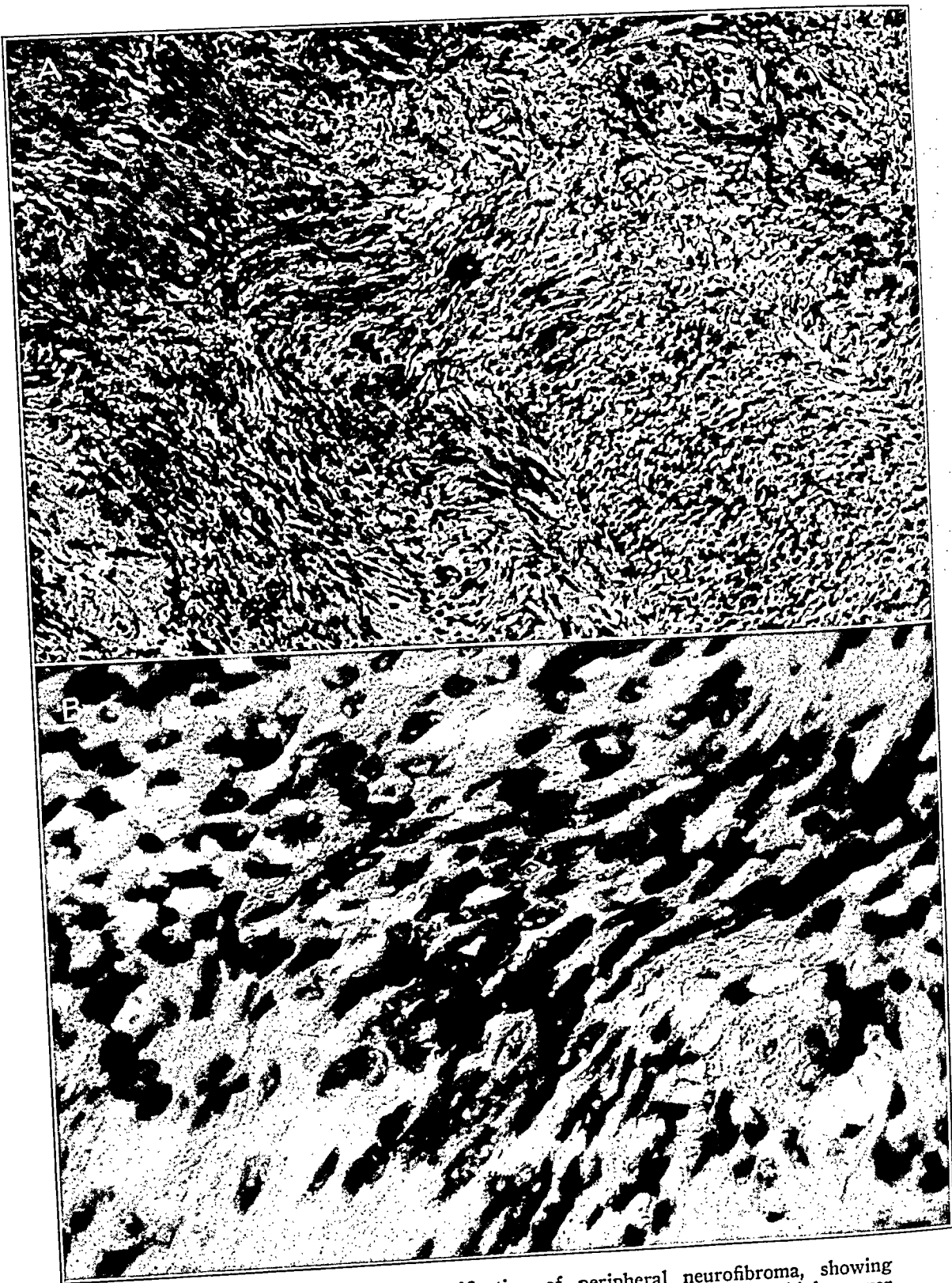


Fig. 5.—*A*, low power magnification of peripheral neurofibroma, showing the typical patternless arrangement of the connective tissue. *B*, high power magnification of the section in *A*, illustrating palisading of nuclei in a perineurial fibroblastoma.

choroid and, rarely, the ciliary body); the cornea; the tarsal conjunctiva, and, lastly, the bulbar conjunctiva.

The presence of primary tumors of the optic nerve in association with neurofibromatosis has recently received a great deal of attention in the literature (Davis,<sup>4</sup> Gomes<sup>5</sup>). There has been considerable controversy among pathologists concerning the nature of the tumors which accompany the disease, since the cause of neurofibromatosis and related lesions is still unknown. Many authors have asserted that the finding of a tumor of the optic nerve in the presence of neurofibromatosis is merely coincidental and should not be considered a manifestation of the same syndrome. Other workers, among whom are Emanuel<sup>6</sup> and Davis,<sup>4</sup> stated the opinion that the so-called primary tumors of the optic nerve are in many instances only a part of this syndrome.

Del Río-Hortega<sup>7</sup> offered an interesting theory of a common source of origin of tumors of the optic nerve and tumors of the peripheral nerves. He asserted that the oligodendroglia of the optic nerve is homologous with the Schwann cells of the peripheral nerves; since the two cellular elements maintain the myelin sheath of the nerve, he suggested that these homologous structures, although differing greatly in their anatomic architecture, could be affected simultaneously by a common cause.

Verhoeff,<sup>8</sup> in 1932, stated that in a possible 4 cases "a glioma of the optic nerve was associated with von Recklinghausen's disease." He added, however, that "it does not follow that the tumor of the optic nerve is related to fibroma of the peripheral nerves, except to the extent that both may be dependent upon some congenital developmental anomaly."

The growths in the optic nerve heads in the present case resembled the picture described by Stallard, with several minor exceptions. The nasal halves of the elevated disks had a grayish red coloration. This hyperemic tinge was probably due to the presence of newly formed capillaries, intermingled with the new growth. Verhoeff found that some

4. Davis, A. F.: Primary Tumors of Optic Nerve, Tr. Sect. Ophth., A. M. A., 1939, p. 145.

5. Gomes, J. P.: Tumors of the Optic Nerve, Am. J. Ophth. **24**:1144, 1941.

6. Emanuel, C.: Ueber die Beziehungen der Sehnervengeschwülste zur Elephantiasis neuromatodes und über Sehnervengliome, Arch. f. Ophth. **53**:129, 1902.

7. del Río-Hortega, P.: Tercera apartación al conocimiento monfológico e interpretación funcional de la oligodendroglia, Mem. Soc. españ. de hist. nat. **14**:5, 1928.

8. Verhoeff, F. H.: Tumors of the Optic Nerve, in Penfield, W.: Cystology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1029.

Left eye: The fundus of the left eye closely resembled that of the right eye. The disk, which was elevated 3 D., had the same color pattern as that of the right eye. No pathologic change was noted in the macula. Several small, grayish white patches, with pigment, were scattered in the superior nasal quadrant. Yellowish flecks were also present in the inferior nasal quadrant. No cholesterol crystals were apparent.

Perimetric studies (May 5): The blindspots were enlarged (fig. 7), the right blindspot being slightly larger than the left. A small, absolute central scotoma was demonstrated in the right eye; no central scotoma was observed in the left eye. The peripheral fields were normal.

*Diagnoses.*—(1) The diagnoses were neurofibroma of the optic papilla, bilaterally associated with medullated nerve fibers and choroidal sclerosis; (2) incipient sclerosis of the retinal arterioles, without hypertension, and (3) central chorioretinitis of the right eye.

*Subsequent Course.*—The patient was observed until June 1, 1946, when he showed no obvious alterations in his physical or ophthalmic status. On June 5, 1946 I received my discharge from the Army and therefore was unable to continue my observation and study of the patient.

#### COMMENT

In 1882, von Recklinghausen described a disease characterized by the classic signs of tumors of the skin and the peripheral nerves with cutaneous pigmentation (café au lait patches). The growths, which were referred to as neurofibromas, were present in and beneath the skin and involved various parts of the body. Since the nerve tissue in any part of the organism may become involved in this disease, the picture is often bizarre. Neurofibromatosis is congenital. The disease shows a hereditary disposition, since it occurs irregularly through several generations: Abortive and monosymptomatic forms have been mentioned. In other cases reported in the literature, skeletal involvement,<sup>2</sup> psychic disorders, intracranial lesions, lesions of the cranial and spinal nerves, disturbances of the glands of internal secretion and hepatomegaly and splenomegaly<sup>3</sup> have been described: The first manifestation may occur at birth or in early life. The tumors are small and usually increase in size slowly, their growth showing a parallelism with the normal growth of the body. Often at puberty the growth of the tumors becomes accelerated, producing symptoms.

When the ocular structures and their adnexa are involved in neurofibromatosis, the parts attacked, in the order of frequency, are the eyelids and the optic nerve; the orbit; the retina; the uvea (iris,

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2. Copeland, M. M.; Craver, L. F., and Reese, A. B.: Neurofibromatosis with Ocular Changes and Involvement of the Thoracic Spine: Report of a Case, *Arch. Surg.* 29:108 (July) 1934.

3. Billow, B. W.: Von Recklinghausen's Neurofibromatosis; A Case of Hepatomegaly and Splenomegaly, *Am. J. Surg.* 61:128, 1943.

neurofibroma. The projecting mass was wedged laterally, involving all the layers of the retina. Reese referred to the alterations in the optic nerve in Wheeler's case<sup>12</sup> as neurofibromatous. Since microscopic studies in my own case were impossible, it is difficult to state from the clinical findings whether the condition was a true neurofibromatous tumor of the optic nerve or a type of gliomatous growth, as described by Davis.<sup>4</sup>

Cases of papilledema were reported by Stern,<sup>13</sup> Lisch<sup>14</sup> and Schmidt.<sup>15</sup> Wiegmann,<sup>16</sup> Fuchs<sup>17</sup> and Holmström<sup>18</sup> described optic nerve atrophy in association with neurofibromatosis. The atrophy was either the result of a simple descending type of degeneration or was postneuritic. The normal spinal fluid and normal pressure, the normal roentgenograms of the skull and the absence of progressive or receding changes in the elevated disks in my case were against the diagnosis of papilledema. Roentgenograms of the optic foramens were not taken.

Goldstein and Wexler<sup>19</sup> described a case of neurofibromatosis in which melanosis of the uveal tract and melanomas of the iris were the outstanding ocular lesions. In addition, the patient had a fibrosarcoma and a distinct endocrinal dysfunction. Again, in 1932, the same authors<sup>20</sup> described a case in which a spongioneuroblastoma of the left optic nerve was associated with the diffuse neurofibromatosis of von Recklinghausen.

It is interesting to note that buphthalmos is not infrequently associated with neurofibromatosis. The buphthalmic condition is attributed by some authors to a congenital defect in the filtration angle and mal-

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12. Wheeler, J. M.: Plexiform Neurofibromatosis (von Recklinghausen's Disease) Involving the Choroid, Ciliary Body and Other Structures, *Tr. Am. Ophth. Soc.* **34**:151, 1936.

13. Stern, R. O.: Tumor of Optic Nerve, Chiasm, and Thalamus, *Proc. Roy. Soc. Med.* **30**:1096, 1937.

14. Lisch, K.: Ueber Beteiligung der Augen bei der Neurofibromatosis (Recklinghausen), *Ztschr. f. Augenh.* **93**:137, 1937.

15. Schmidt: Multiple Neurinome mit Beteiligung der Papillen, *Klin. Monatsbl. f. Augenh.* **101**:115, 1938.

16. Wiegmann: Ein Fall von Recklinghausenscher Krankheit mit Komplikationen seiten der Augen, *Klin. Monatsbl. f. Augenh.* **68**:395, 1923.

17. Fuchs, A.: Ueber einfache Opticusatrophie bei Recklinghausenscher Erkrankung, *Wien. klin. Wchnschr.* **50**:291, 1937.

18. Holmström, M.: Zwei Fälle von Exophthalmos bei Neurofibromatosis Recklinghausen, *Acta. ophth.* **6**:403, 1928.

19. Goldstein, I., and Wexler, D.: Melanosis Uveae and Melanoma of the Iris in Neurofibromatosis, *Arch. Ophth.* **3**:288 (March) 1930.

20. Goldstein, I., and Wexler, D.: Spongioneuroblastoma in Neurofibromatosis (Recklinghausen), *Arch. Ophth.* **7**:259 (Feb.) 1932.



neurofibromatous tumors tend to become vascularized in time. I do not believe that this angiomatous feature is unusual, since the phakomatoses are closely related (Moolten<sup>9</sup>), and it is not surprising to observe occasional mixed forms. It has been shown that there are numerous points of resemblance between the tuberous sclerosis complex and von Recklinghausen's multiple neurofibromatosis. The lesions are regarded as hamartomas, and not true neoplasms.

In the present case, the temporal halves of the elevated growths showed moderately thickened and well delineated, medullated nerve fibers. The terminal striations presented thickened, individual nerves and appeared decidedly wider than the usual fine, feathery striations which one often observes in the classic picture of the fundus. Reese and associates<sup>2</sup> described the presence of medullated nerve fibers in both eyes of a patient with neurofibromatosis. Fischer<sup>10</sup> found medullated nerve fibers in the retinas of 4 of 12 patients with generalized neurofibromatosis. He was inclined to believe that the incidence of medullated nerve fibers in the retina was greater among patients with definite abnormalities of the central nervous system or with psychopathic disturbances. This view has been substantiated in several cases and is readily applicable to the present case, since mental retardation was demonstrated conclusively by the Bellevue-Wechsler tests. Manz<sup>11</sup> found retinal medullation in 4 of 130 inmates of an asylum. On the other hand, he performed a routine ophthalmic examination of 3,250 patients and uncovered only 1 case of medullated nerve fibers in the retina.

The yellowish flecks seen in the fundi closely resembled those described by Stallard. The attenuation and the increase in the central light reflexes of the retinal arteries, the cholesterol crystals and the early choroidal sclerosis favored the additional diagnosis of early retinal arteriosclerosis. The small, chorioretinitic patches were presumably old, healed degenerative lesions, a picture not infrequently seen with the phakomatoses. There were no lesions in the retina which resembled tuberous sclerosis.

Stallard described a hemispherical mass projecting from the disk. It was grayish, with a nodular surface. Its outline and edges were ill defined. Some small, irregular flecks were present in the retina, adjacent to the disk. Histologic sections demonstrated irregular-shaped clumps and sweeping bundles of neurocytes, neurofibrils and many small cysts. The microscopic picture was characteristic of a

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9. Moolten, S. E.: Hamartial Nature of the Tuberous Sclerosis Complex and Its Bearing on the Tumor Problem, *Arch. Int. Med.* **69**:589 (April) 1942.

10. Fischer, H.: Beitrag zur Recklinghausenschen Krankheit: Missbildungen am Auge, besonders die markhaltigen Nervenfasern der Netzhaut, *Dermat. Ztschr.* **42**:143, 1924.

11. Manz, cited by Fischer.<sup>10</sup>

Again, the round, homogeneous, extrapleural mass in the apex of the right lung shown in the roentgenogram was probably a benign tumor. Originally, the possibility of a tumor of the superior pulmonary sulcus was entertained but was discarded, since the characteristic clinical and roentgenographic signs were wanting. In the differential diagnosis, one must also consider the possibility of a primary, apical carcinoma or a sarcomatous infiltration of the ribs. In repeated roentgenologic studies, no demonstrable alterations were found in the apex of the right lung or in the neighboring tissues. A biopsy specimen was not taken, but, because of the benign character of the growth, and the widespread, multiple involvement in this unusual case, a diagnosis of neurofibroma was made. It was suggested that the tumor might have arisen from one of the cords of the brachial plexus.

Davis advised that in all cases of tumor of the optic nerve a systematic investigation be made for all the signs of neurofibromatosis—specifically, soft nodules of the skin; café au lait spots; possible lesions of the choroid, ciliary body and iris in association with buphthalmos; skeletal deformities, and neurofibromatosis, especially of the eyelids and the orbital nerves. On the other hand, I suggest that in all cases of neurofibromatosis a thorough examination be made of the eyes, including roentgenograms of the skull and optic foramina, exophthalmometric readings and air studies of the orbital spaces.

#### SUMMARY

A case of bilateral tumor of the optic nerve, involving the papilla, associated with neurofibromatosis is reported. Unusual associated findings were (a) a neurofibromatous growth in the apex of the right lung, (b) bilateral acoustic neuroma, (c) mental retardation and (d) medullation of the retinal nerve fibers.

Neurofibromatosis is briefly discussed with respect to its etiology, incidence, pathology, clinical manifestations, diagnosis and differential diagnosis.

Other ocular lesions associated with neurofibromatosis are described.

The relation of primary tumors of the optic nerve to neurofibromatosis, as discussed by Davis, is briefly reviewed.

It is suggested that all patients with neurofibromatosis be subjected to a complete, and most critical, ophthalmologic examination.

development of the spaces of Fontana. The iris is usually adherent by broad synechias to the posterior margin of the cornea.

In the first biopsy of peripheral nerve in the present case, the diagnosis was perineurial fibroblastoma. In another biopsy of nerve, on May 27, 1946, the microscopic diagnosis was neurofibroma. This discrepancy is understandable in view of the frequent observation of perineurial fibroblastic growths in the center of neurofibromas, as Penfield<sup>21</sup> and others have shown. The connective tissue in a neurofibroma of a peripheral nerve shows a characteristic patternless arrangement. The nuclei are not arranged in any particular order. A great deal of variation in the microscopic appearance of these tumors is likely to be present. The presence of nerve fibers within the tumor may be considered pathognomonic of neurofibroma. The appearance of the tumor in general is like a reaction about nerve fibers, rather than a neoplastic growth. Neurofibromas are benign and do not metastasize. They usually involve the peripheral nerves. The outstanding histologic characteristic of perineurial fibroblastomas is the nature of the collagen fibers. They are long and of even caliber and tend to be parallel. The nuclei are arranged in long rows and frequently give the appearance of Verocay's palisades. These tumors are neoplastic and are usually present in nerve roots.

The gradual diminution of hearing in my case over a period of nine years, in association with the widespread multiple manifestation of neurofibromatosis, strongly favors the diagnosis of bilateral acoustic neuroma. Frazier and Gardner<sup>22</sup> reported on a remarkable family in which numerous members had bilateral deafness. Later studies revealed bilateral acoustic neurofibromas in these persons. Steurer<sup>23</sup> reported 2 cases of neurofibromatosis in which the acoustic nerves were involved. In Katzenstein's<sup>24</sup> case there was similar infiltration of the acoustic nerve. Shapland and Greenfield<sup>25</sup> reported a case of bilateral deafness, due to tumors in the cerebellopontile angles.

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21. Penfield, W.: *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 967.

22. Frazier, C. H., and Gardner, W. J.: *Bilateral Acoustic Neurofibromas: Clinical Study and Field Survey of a Family of Five Generations with Bilateral Deafness in Thirty-Eight Members*, *Tr. Am. Neurol. A.* **55**:187, 1929.

23. Steurer, O.: *Ueber Beteiligung des inneren Ohres und des Hörnerven bei multipler Neurofibromatosis*, *Recklinghausen, Ztschr. f. Hals-, Nasen- u. Ohrenh.* **4**:130, 1922.

24. Katzenstein, R.: *Ueber innere Recklinghausensche Krankheit (Endotheliome, Neurinome, Gliome, Gliose, Hydromyelic)*, *Virchows Arch. f. path. Anat.* **286**:42, 1932.

25. Shapland, C. D., and Greenfield, J. G.: *Neurofibromatosis with Meningeal Tumor Involving the Left Optic Nerve*, *Tr. Ophth. Soc. U. Kingdom* **55**:257, 1935.

two imperfections: At times the electrode has to be steadied during the treatment; furthermore, as the chimney containing the solution is open at the top, the liquid tends to escape around the base.

An improved contact lens electrode would, therefore, have to incorporate modifications to meet the following criteria: 1. The possibility of injury to the cornea must be completely excluded by an arrangement which effectively keeps the electrode from touching the tunic of the eye, and permits only the medicament to come in direct contact with the cornea. 2. The instrument must be constructed in such a manner that, once installed, it would stay in place without requiring further support by

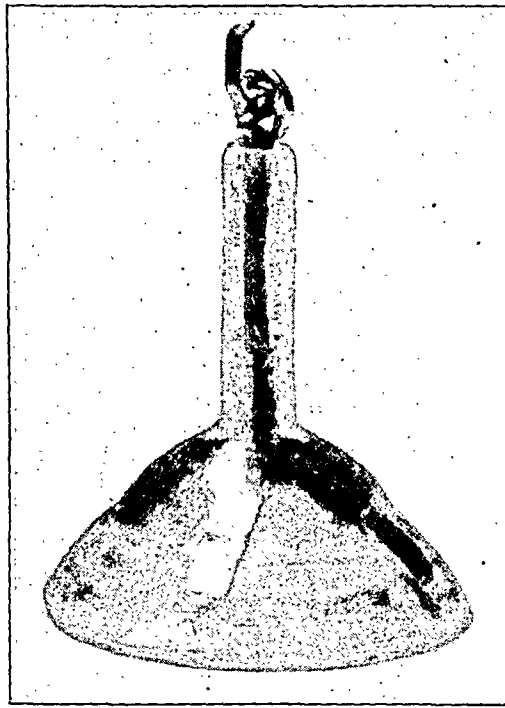


Fig. 1.—Lateral view of contact lens electrode. A platinum electrode is accommodated between two contact lenses, which are fused together. The electrode is connected with a supply wire (not shown) through an adapter, contained in a sleevelike extension.

the operator. 3. Finally, the amount of leakage of medicinal solution must be reduced to a minimum.

With this object in mind, an electrode has been devised consisting of two contact lenses which are fused together. The inner contact lens has a corneal portion with a radius of 7.5 mm. A curve of this diameter has proved most satisfactory in 90 per cent of all contact lenses fitted<sup>7</sup> and provides sufficient space between lens and cornea to accommodate

7. Obrig., T. E.: *Contact Lenses*, Philadelphia, The Chilton Company, 1942, p. 256.

# CONTACT LENS ELECTRODE FOR IONTOPHORESIS

PAUL TOWER, M.D.

LOS ANGELES

**E**XPERIENCE with iontophoresis goes back to the end of the last century. In recent years, sodium sulfathiazole<sup>1</sup> and a number of other substances<sup>2</sup> have been recommended as therapeutic agents. The procedure, however, has been much more widely discussed since the introduction of penicillin<sup>3</sup> led to spectacular results.

The electrodes used in iontophoresis range from a medicated piece of cotton, placed between a small metal plate and the eye, to a cylindric glass tube, adapted to fit the shape of the cornea. Sometimes a plain probe is employed, such as Hamberger's electrode, consisting of a piece of cotton, which has been saturated with the medicinal solution, wrapped around the end of a thin carbon rod.<sup>4</sup>

All these types of electrodes must be held in position by the operator throughout the treatment, since they are not so devised that they will stay in place unsupported. Furthermore, they are difficult to manipulate and are apt to cause injury to the epithelium of the cornea, even when handled with care. By reason of these defects of iontophoresis, Duncan<sup>5</sup> suggested application of penicillin by means of a corneal bath. Selinger,<sup>6</sup> however, succeeded in devising a greatly improved electrode. The instrument is essentially a contact lens base with a narrow chimney extending from its center. But the new instrument appears to have

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1. Boyd, J. L.: Sodium Sulfathiazole Iontophoresis, *Arch. Ophth.* **28**:205-213 (Aug.) 1942.

2. Fleming, N.: Iontherapy (Ionic Medication, Iontophoresis, Ionisation) as an Aid in Ophthalmic Therapeutics, *Brit. J. Ophth.* **27**:354-367 (Aug.) 1943.

3. von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, *Arch. Ophth.* **31**:1-7 (Jan.) 1944. Dunnington, J. H., and von Sallmann, L.: Penicillin Therapy in Ophthalmology, *ibid.* **32**:353-361 (Nov.) 1944. Wright, R. E., and Stuart-Harris, C. H.: Penetration of Penicillin into the Eye, *Brit. J. Ophth.* **29**:428-436 (Aug.) 1945. von Sallmann, L.: Penetration of Penicillin into the Eye, *Arch. Ophth.* **34**:195-201 (Sept.) 1945.

4. Klein, M., in Ridley, F., and Sorsby, A.: *Modern Trends in Ophthalmology*, New York, Paul B. Hoeber, Inc., 1940, p. 510.

5. Duncan, H. A. G.: Plastic Corneal Bath for Application of Penicillin, *Arch. Ophth.* **33**:3-314 (April) 1945.

6. Selinger, E.: *Office Treatment of the Eye*, Chicago, The Year Book Publishers, Inc., 1947, p. 519.

keep the contact lens well centered over the cornea, the patient should fix the gaze of the other eye on his hand, or some other object, held straight in front of him at close range.

The success of treatment depends on the presence of a sufficient amount of penicillin at the holes within the inner lens, where the current passes from the electrode to the cornea. For this reason, it matters little whether air has entered into the space between lens and cornea, or whether, inadvertently, the cup has not been completely filled with the solution. If part of the liquid should leak out, enough will remain in the limbal portion of the lens to permit passage of the current into the cornea through at least one or two holes. But even if, accidentally, no fluid should have been left between the inner lens and the cornea, the possibility of injury is excluded because the metal of the electrode can never touch the globe.

A contact lens electrode of the type described here has been used successfully in a considerable number of cases. The opinion may be expressed that the most serious shortcomings inherent in the electrodes formerly used have been eliminated in the new appliance, with the hope that antibiotic ion therapy, as well as iontophoresis using other medicinal solutions, has been made a safer procedure.

610 South Broadway (14).

the medicinal solution. Four holes with a diameter of 2 mm. are drilled into the limbal portion of the inner lens, at points equidistant from the center.

The outer contact lens fits snugly over the inner one, but the two are fused together in such a manner as to leave enough room to accommodate a platinum electrode with four prongs, which are long enough to extend over the holes drilled into the inner contact lens. In the center of the outer contact lens, an aperture communicates with a sleeve-like extension containing an adapter which connects the platinum electrode with a supply wire.

Introduction of the electrode proceeds with the patient either sitting up or lying on his back. As a rule, no anesthesia is required, but instillation of a drop of any of the customary local anesthetics may be indicated with nervous patients, or whenever the eye is hypersensitive.

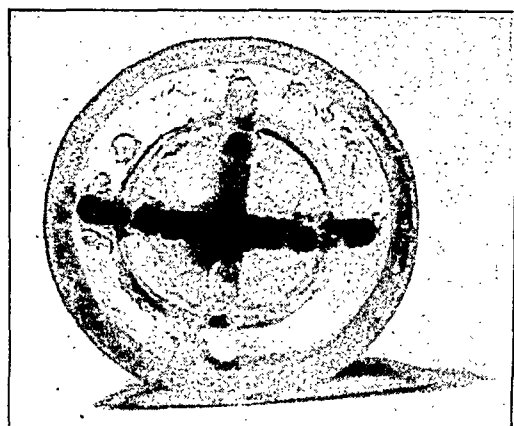
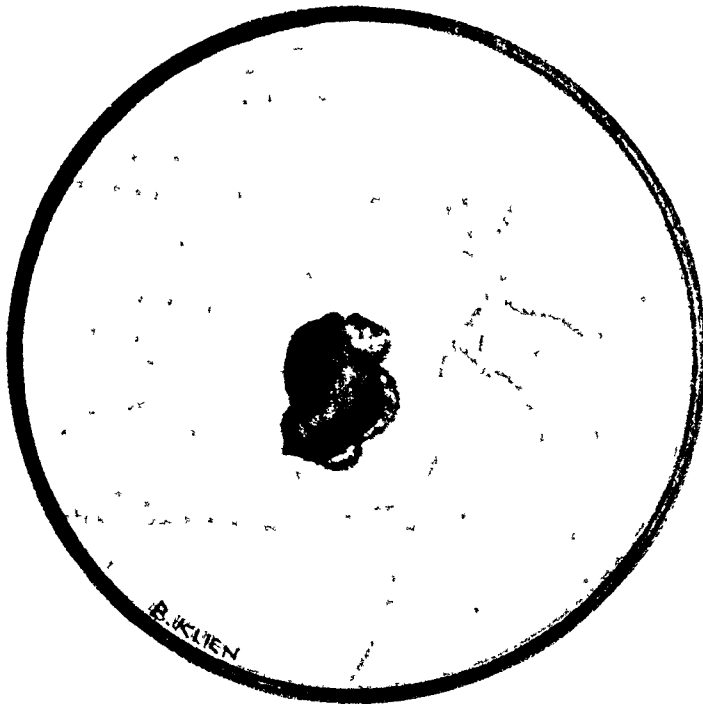


Fig. 2.—View into the cup of the contact lens electrode. The four-pronged platinum electrode is separated from the cornea by the inner contact lens. The current passes through the four holes drilled into the limbal portion of the inner lens, corresponding to the four prongs of the electrode. No direct contact between electrode and cornea can take place.

The penicillin solution is placed in the cup of the inner lens and the appliance inserted like an ordinary contact lens. While holding the electrode by the stem, its upper edge is inserted under the upper lid, with the patient looking downward. The lower lid is then retracted, whereupon the contact lens falls into place. If it is preferred, the medicinal solution may also be introduced after the contact lens electrode has been inserted. The liquid is then instilled with a curved medicine dropper or an irrigator of the type used for the anterior chamber; for this purpose the temporal edge of the lens is slightly lifted and quickly replaced after the solution has been introduced. Irrespective of whether the patient has been sitting up or lying down during introduction of the electrode, the appliance will stay in place during treatment. In order to



Drawing of the fundus showing the cyst floating free in the vitreous. The dark area posterior to the cyst is its shadow on the fundus.



# CONGENITAL CYST OF THE VITREOUS

Report of a Case

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**C**YSTS in the vitreous body of the eye are so uncommon as to be ophthalmologic curiosities. A review of the literature in 1939<sup>1</sup> disclosed only 18 cases of free floating, congenital cysts of the vitreous. Since then, several cysts associated with inflammatory or degenerative processes or congenital cysts attached to the optic disk, hyaloid or other retinal blood vessels have been described.<sup>2</sup> I have found a second congenital cyst floating free in the vitreous nearly identical with the one I previously described.<sup>1</sup>

## REPORT OF CASE

*History.*—R. T., a boy aged 9, was first brought to my office in November 1947. His parents had observed him turning his head to the side to look at a distant object, such as the blackboard at school. An ophthalmologist had fitted him with glasses the previous year, without relief. Neither the boy nor his parents had any explanation for the turning of his head except that he had never been able to see much out of his left eye.

*Examination.*—The patient was intelligent, cooperative and of normal appearance. Both eyes appeared normal; there was no apparent squint or facial asymmetry. Vision was 20/20 in the right eye and 5/200 in the left eye. The pupils were regular and equal and reacted to light and in accommodation.

The anterior chamber, cornea and iris of both eyes appeared normal. The eye-ground of the right eye was normal except for a moving, dark red shadow. The optic disk was normal; there were no prepapillary loops or membrane; the vessels were of normal appearance; the macula and the periphery of the retina were not remarkable.

A round cyst floated in the middle of the vitreous and cast a moving, dark red (called "dark" in legend) shadow on the fundus. With indirect ophthalmoscopy, it appeared as a shadowy, gnarled, floating, oval cyst with a wrinkled surface. It moved and floated about with movements of the eye but returned to its original position near the center of the globe as the movement ceased. With direct ophthalmoscopy, it came into sharpest focus with a +16 D. lens. The cyst was swarthy, bumpy and nodular; it seemed semitransparent, as dark, irregular streaks with lighter background covered its wrinkled surface. With the slit lamp, or, better, with a flashlight, it could be visualized as of yellowish gold color with crinkly surface.

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1. Cassady, J. V.: Congenital Cyst of the Vitreous, Arch. Opth. **21**:45-50 (Jan.) 1939.

2. Saenz Canales, J.: Formaciones quísticas en el cuerpo vitreo; un caso clinico, An. Soc. mex. de oftal. y oto-rino-laring. **17**:123-139 (July-Aug.) 1942.

Neither remnants of the hyaloid artery nor Cloquet's canal could be visualized except for the cyst in the vitreous. Refraction of each eye with homatropine cycloplegia showed:

Right eye: +1.00 D. sph.; vision 20/20

Left eye: -14.00 D. sph.  $\ominus$  +4.00 D. cyl., ax. 75; vision 5/200

The left eye had a myopic fundus with an elongated, elliptic disk and a scleral crescent on its temporal side. The vitreous, media, vessels, macula and periphery of the retina appeared normal. The eye was amblyopic without demonstrable anomaly except for the high myopic astigmatism.

The cyst of the right eye was irregular, entirely free floating and unattached by any strand. It rose, turned, settled down, moved to either side but always returned nearly to its original position in or close to Cloquet's canal and the primary vitreous.

After I had described it to Prof. Ida Mann, she wrote: "I suspect the cyst represents a persistence and cystic dilatation of a portion of the anterior end of the neurologic sheath of the hyaloid artery. As it is unattached, but remains in the center of the vitreous, it is presumably in Cloquet's canal, and so must have something to do with vascular remains."

#### COMMENT

As I previously observed,<sup>1</sup> the apparent pigmentation of the cyst is an illusion, owing to its being seen in silhouette against the light reflected from the illuminated eyeground. Both the cysts described were visible with direct light, as were those of Hurwitz and Meding. They were not dark, but had a hyaline gilded or yellow surface. This, together with their location near the center of the vitreous in Cloquet's canal, suggests that they were a part of the neurologic element of the primitive Bergemeister's papilla, or a remnant of the covering of the hyaloid artery.

The original cyst I described maintains the same appearance as that on first examination, ten years ago, and is almost identical with the one reported here. The fact that I could not easily find it again when I examined the patient recently, suggests that such cysts may be often missed.

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environment) could enough oxygen pass through to keep the endothelium viable.

Fischer<sup>2</sup> (1930) studied these changes in vivo by the use of a glass chamber which fitted snugly to the luxated eye. Known gases were introduced, and samples could be removed for analysis at the end of an experimental period. Fischer corroborated the findings of Bullof and Lor when he noted an increase in the oxygen consumption and in the production of carbon dioxide following the removal of epithelium from the living eye. He came to the conclusion that this layer acts as a barrier to the exchange of gases without itself entering into the process of utilizing oxygen or producing carbon dioxide. He reasoned thus because he did not find a lowering of oxygen consumption or carbon dioxide production accompanying deepithelization. Finally, he stated the belief that the oxygen was utilized by the endothelium and the carbon dioxide produced passed anteriorly to the outside atmosphere. This view was substantiated by the experimental demonstration of corneal opacities in an atmosphere of pure carbon dioxide, which (according to Fischer) hinders the diffusion of excretory gases from the cornea and results in endothelial necrosis. Thus, Fischer envisaged the combination of the corneal epithelium, glass membranes and stroma as a glorified blood capillary wall with respect to the exchange of gases concerned with the endothelial respiration. This view was undoubtedly influenced by the incorrect belief which prevailed at the time, that the endothelium was the all-important structure for the control of fluid traffic through the cornea. Fischer's work was justifiably criticized by Bakker<sup>3</sup> (1947) as not being performed under optimal physiologic conditions. While Bakker unjustly cited Fischer's statements out of context, he appeared to be fair in stating that luxated eyes on which were placed snugly fitting bell type chambers, compressing ocular circulation, were not under normal in vivo conditions. Furthermore, he pointed out Fischer's complete indifference to the circulation of the limbal arcade. It is interesting to note that from the experiments performed by Bakker, which were also unphysiologic, the same results were obtained in an atmosphere of 100 per cent carbon dioxide, although the interpretation is quite different. This investigator, who had earlier (Bakker,<sup>4</sup> 1941) found carbonic anhydrase in the cornea and assumed it was present to facilitate the removal of carbon dioxide in the absence of blood vessels, decided to reinvestigate Fischer's work on the selective permeability of

2. Fischer, F. P.: Ueber den Gasaustausch der Hornhaut mit der Luft, Arch. f. Augenh. **102**:146, 1930.

3. Bakker, A.: Some Researches on the Respiration of the Cornea in Albino Rats, Brit. J. Ophth. **31**:100, 1947.

4. Bakker, A.: Der Kohlensäureanhydrasegehalt verschiedener Augengewebe einiger Säugetiere, Ophthalmologica **102**:351, 1941.

# Ophthalmologic Reviews

## METABOLISM OF THE CORNEA

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SINCE the greater part of the cornea is remotely situated from the blood stream, this area may present unique mechanisms for the transfer of metabolites and excretory products. This tissue is avascular, but it is surrounded at its periphery by intravascular and extravascular fluid. Furthermore, it is bathed anteriorly and posteriorly with continuously circulating fluids. It is exposed to the atmosphere in the waking hours and yet survives many hours when sealed by the lids during sleep. Even the relatively anaerobic environment in the conjunctival sac of deep-sea-diving mammals and hibernating land forms does not irreversibly disturb the functions of the cornea. It is pertinent, therefore, to inquire: How does the cornea respire? Are its cellular metabolic mechanisms similar to those found in other tissues? If not, in what way do they differ? This report is an attempt to outline the experimental investigation which has been undertaken on these problems, in the hope that a concentration and evaluation of the available literature will assist in the approach to unsolved problems which confront the experimentalist today. Discussions of the various factors involved will be placed under the appropriate headings when possible, but there are many instances of overlapping, and in these cases the discussion appears under the heading of the most important factor involved in a given experiment.

### ATMOSPHERIC ENVIRONMENT OF THE CORNEA

As early as 1899, Bullot and Lor<sup>1</sup> transplanted eyes into peritoneal cavities and found that the corneas became opaque in the presence of the low oxygen tensions existing there, but the opacities were limited to areas under intact epithelium. The scraped areas (without epithelium) remained clear. From this study it was concluded that the epithelium withheld oxygen from the endothelium and that only in the presence of the relatively higher oxygen tension (such as exists in the normal

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1. Bullot, G., and Lor, L.: De l'influence exercée par l'épithélium de la cornée sur l'endothélium et le tissu cornéens de l'œil transplanté, Bull. Acad. roy. de méd. de Belg. 13:421, 1899.

element. However, there is a lack of information on the relation of such tissues as mucous membranes to atmospheric oxidation. The burden of proof is on those who assume the corneal tissue to be unique in its procurement of oxygen directly from the atmosphere, as compared with other tissues, which are supplied exclusively by the oxygen borne in the blood stream. Therefore, the question is still unsolved.

#### METABOLISM IN THE VARIOUS CORNEAL STRATA

As already mentioned, Bullot and Lor<sup>1</sup> (1899) and also Bullot<sup>6</sup> determined that the endothelium requires considerable oxygen for its maintenance. These experimenters described a "wave of asphyxia" in the corneal endothelium, extending from the periphery toward the center in the presence of a decreased oxygen tension. However, just the reverse occurred in a toxic oxygen excess: the central endothelium died early, whereas the periphery showed relative resistance. According to Bakker<sup>3</sup> (1947), Bullot's experiments suggested that oxygen from the atmosphere was utilized by the endothelium; but, since the eyes were enucleated and the corneal epithelium was scraped off, the conditions were too far from physiologic to permit one to conclude whether or not oxygen from the air moves toward the anterior chamber in living animals.

Fischer<sup>2</sup> (1930) presented evidence of the respiratory activity of the endothelium in the cornea. He dismissed the epithelium as an inactive participant. Rauh's<sup>7</sup> (1934) results differed from Fischer's. By the reduction of nadi reagent (equal parts of 1 per cent aqueous solutions of dimethylparaphenylendiamine and alpha-naphthol), he showed that all cells of the cornea entered into a definite respiratory cycle. These results, though crude, were substantiated in 1935 by Kohra<sup>8</sup> (table), who was the first to attempt to measure accurately the respiration of the cornea by the Barcroft-Warburg<sup>9</sup> (1926) technic. Kohra's article was published in Japanese, but Süllman<sup>10</sup> (1938) and Weekers<sup>11</sup> (1940) referred to the work and stated that a corneal opacity

6. Bullot, G.: (a) Sur la physiologie de l'épithélium cornée: imperméabilité relative à l'oxygène, *Bull. Acad. roy. d. sci. de Belg.*, 1900, p. 887; (b) Bruxelles, Hayex, 1900; (c) On the Action of Oxygen at Low and High Pressure upon the Corneal Endothelium, *J. Physiol.* **31**:359, 1904.

7. Rauh, W.: Beitrag zur Zellatmung der Hornhaut, *Ber. ü d. Versamml. deutsch. ophth. Gesellsch.* **50**:212, 1934.

8. Kohra, T.: Ueber den Stoffwechsel der Hornhaut, *Acta. soc. ophth. jap.* **392**:1429, 1935; German summary, p. 107.

9. Warburg, O.: *The Metabolism of Tumors*, translated by F. Dickens, New York, Richard R. Smith, Inc., 1931.

10. Süllman, H.: *Biochimie des Auges*, *Ophthalmologica* **96**:37, 1938.

11. Weekers, R.: *Biochimie de la cornée normale et pathologique*, *Ophthalmologica* **100**:136, 1940.

the cornea in the living eye. His technic of maintaining an animal in a closed chamber with artificial respiration through taps to the outside eliminated some of the artefacts produced by Fischer's technic, but it is important to realize that even here the eyes might not have been under strictly optimal physiologic conditions. The animals were subjected to general anesthesia, and the lids were sutured open throughout the experiment. At the beginning of the procedure the entire animal was completely submerged in a physiologic saline fluid, and the environmental gases were saturated with water vapor, which may have also altered the normal *in vivo* conditions. As in Fischer's experiments, no changes were noted in the corneas remaining in a pure nitrogen atmosphere for twelve hours. Therefore, it was concluded that the cornea did not obtain oxygen from the atmosphere, and the fact that diving whales and sleeping persons do not experience corneal changes was held to be consistent with these findings. Bakker expressed doubt of the selective permeability of the cornea to carbon dioxide; he demonstrated that the cornea (as shown by histologic examination) could be maintained at carbon dioxide (8 per cent carbon dioxide; 92 per cent nitrogen) tensions much higher than those of the body, and that it became opaque only in an atmosphere of 100 per cent carbon dioxide. Thus, the corneal changes were not caused by an impediment to removal of carbon dioxide, but resulted from the toxic effect of the high concentration of carbon dioxide per se.

In a different manner, Gundersen<sup>5</sup> (1938-1939) obtained evidence that the epithelium degenerated when exposed to low oxygen tension. Invariably, the epithelium of autotransplants of cornea into the anterior chamber disappeared in the aqueous substrate. This was noted even when the transplant was nourished by the iris, a phenomenon which occurred in all but one experiment. The stroma remained intact; indeed, the endothelium flourished in that it enveloped the transplants in all the experiments. He concluded that the epithelium utilized oxygen directly from the atmosphere.

*Comment.*—The observations of Bullo and Lor and the findings of Gundersen might possibly be ascribed to other physiologic phenomena, such as osmotic effects, rather than to gas tensions. Both Fischer and Bakker demonstrate the toxic effects of high carbon dioxide tensions, but the latter, in his nitrogen experiment, clearly proved the absence of any effect due to low oxygen tension. Can the corneal strata utilize oxygen directly from the atmosphere? Most tissues in the mammalian body depend on oxygen from the blood stream as their source of this

5. Gundersen, T.: (a) Results of Autotransplantation of Cornea, *Tr. Am. Ophth. Soc.* **36**:207, 1938; (b) Vascular Obliteration for Various Types of Keratitis: Its Significance Regarding Nutrition of Corneal Epithelium, *Arch. Ophth.* **21**:76 (Jan.) 1939.

corneas, and he decided that it was impossible to measure the respiration of the endothelium alone because the trauma involved in its removal lowered its respiratory capacities. However, he stated the belief that the endothelium must have an active metabolism, since it alone was responsible for the uptake of oxygen after the epithelium was removed, as no respiration could be demonstrated from the parenchyma alone. He attributed a definite consumption of oxygen and breakdown of carbohydrate to the epithelium. Orzalesi concluded that the metabolism of the cornea varied inversely with the mass, since the main bulk of the cornea consists of relatively inert stroma, the epithelium making up a small portion of the total volume or weight, and the endothelium still less (table).

Fischer<sup>14</sup> (1940) reported values for the various portions of the cornea which differed from those in his earlier work and estimated that the oxygen intake ( $\text{QO}_2$ ) of the epithelium and of the endothelium was equal to 3.5 to 4.5 times that of the whole cornea (table). Furthermore, both layers showed considerable aerobic and anaerobic glycolysis. He concluded, therefore, that the classic view (Duke-Elder,<sup>15</sup> 1933) of a "slow" corneal metabolism was no longer acceptable. He gave values for the various layers but, unfortunately, described neither his technics nor his experimental animals.

Herrmann, Moses and Friedenwald<sup>16</sup> (1942) studied the effects on corneal respiration of local anesthetics and other drugs used topically in ophthalmology. They concluded that the metabolism of the cornea involves glycolysis and oxygen activation (cytochrome-cytochrome oxidase complex and dehydrogenation with intermediate carriers) (table). Cyanide, tetracaine, chlorobutanol, pentobarbital sodium, phenacaine, butacaine sulfate, atropine and cocaine were found to inhibit oxygen consumption of the bovine cornea to varying extents. One human cornea removed with the use of a local anesthesia was also found to be greatly depressed. Ephedrine and urethane (ethyl carbamate), though they readily inhibited the isolated enzyme systems, were without effect on the intact cornea. The authors postulated that this lack of inhibition may have been due to the inability of the pharmacologic agents to reach the enzyme systems in the intact organ, thus suggesting that the cornea may become a valuable tool in the study of respiratory systems. Since tetracaine and chlorobutanol did not affect the oxidation of cytochrome c.

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14. Fischer, F. P., in Ridley, F., and Sorsby, A.: *Modern Trends in Ophthalmology*, New York, Paul B. Hoeber, Inc., 1940, p. 351.

15. Duke-Elder, W. S.: *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1933, vol. 1, p. 471.

16. Herrmann, H.; Moses, S. G., and Friedenwald, J. S.: Influence of Pontocaine Hydrochloride and Chlorobutanol on Respiration and Glycolysis of the Cornea, *Arch. Ophth.* **28**:652 (Oct.) 1942.



was noted in deep layers within three to five hours after the ciliary arteries were ligated. This was ascribed to a decreased endothelial metabolism. Interruption of the pericorneal circulation was without effect. Kohra found that the metabolism of the ciliary arteries remained constant and finally increased, whereas the metabolism of the endothelium fell rapidly. In his opinion, the primary cause of corneal opacity secondary to uveal disease is the lack of nourishment in the endothelium. Kohra compared the respiration of the whole cornea and of the various strata in aqueous and in Ringer's solution and found that the respiration was greater in the former and less in the latter. However, the reverse was true for aerobic glycolysis, while anaerobic glycolysis

### Determinations of Corneal Respiration

Author	Animal	Tissue	QO <sub>2</sub> *	O <sub>2</sub> QM†	N <sub>2</sub> QM‡
Kohra <sup>8</sup> (1935) .....	Rabbit	Entire cornea	-1.56	+1.18	+2.32
		Epithelium	-4.80	+4.60	+8.01
		Stroma	-0.79	+0.73	+1.38
Bessey <sup>12</sup> (1939) .....	Rat	Entire cornea	-4.00	+4.70	+1.05
Orzalesi <sup>13</sup> (1939) .....	Rabbit	Entire cornea	-2.09	.....	.....
Fischer <sup>14</sup> (1940) .....	?	Entire cornea	-1.71	.....	+3.05
		Epithelium	-6.15	+0.42	+2.34
		Stroma	-0.93	+1.59	+8.00
		Endothelium	-7.93	+0.69	+1.40
Herrmann and others <sup>16</sup> (1942)	Cow	Entire cornea	-0.54 (calculated assuming dry weight to be 150 mg.)	+2.50	+10.80
Lee and Hart <sup>18</sup> (1944) .....	Rat	Entire cornea	-2.24 (calculated assuming dry weight to be 1.0 mg.)	1.16 cu. mm. oxygen per cornea	0.44 cu. mm. oxygen per cornea
		Epithelium	1.16 cu. mm. oxygen per cornea	0.44 cu. mm. oxygen per cornea	
		Stroma	-1.03; -3.10; -7.45		
		Endothelium	-0.108; -0.215; -0.201		
Shestericova and Rosenfeld <sup>21</sup> (1946)	?	Entire cornea	0.0; 0.0		
		Epithelium	-0.46		
		Stroma	-6.0 to -8.0 (estimated)		
		Endothelium	-0.15		
Robbie and others <sup>22</sup> (1947) ..	Rabbit	Entire cornea			
		Epithelium			
		Stroma			

\* QO<sub>2</sub> indicates oxygen uptake, expressed in cubic millimeters per milligram per hour.  
 † O<sub>2</sub>QM refers to aerobic glycolysis.  
 ‡ N<sub>2</sub>QM refers to anaerobic glycolysis.

was independent of the medium. He concluded that the susceptibility to damage in experimental mediums was greatest in the endothelium, less in the epithelium and least in the stroma. Bessey<sup>12</sup> (1939) showed that the oxygen consumption of the whole rat cornea was 4 cu. mm. of oxygen per milligram (dry weight) per hour (table), as measured by the Barcroft-Warburg technic. In Gundersen's<sup>5</sup> (1938) opinion, this oxygen consumption was due principally to the active epithelium. Orzalesi<sup>13</sup> (1939) repeated Kohra's work on human, rabbit and rat

12. Bessey, O. A., cited by Gundersen,<sup>5b</sup> p. 80.  
 13. Orzalesi, F.: *Ricerca sulla respirazione e sulla glicolisi della cornea*, Boll. d'ocul. 18:509, 1939; Zentralbl. f. d. ges. Ophth. 44:537, 1940.

Hart and Lee<sup>20</sup> (1945) were unable to confirm the results of Herrmann and his associates concerning the effects of cocaine on the corneal respiration. They found an increase in oxygen uptake by the cornea in the presence of 5 per cent cocaine. However, their studies were made on rat corneas, whereas Herrmann's group employed the bovine cornea. Both groups were agreed on the inhibitory effects of tetracaine and cyanide.

Shesticova and Rosenfeld<sup>21</sup> (1946) investigated the respiration of the cornea during preservation. They reported an increase in respiration during the first six days, but on the seventeenth day the respiration had fallen to about 50 per cent of normal. Their values for oxygen consumption for the various strata are tabulated in the table. They compared Ringer's solution with aqueous as a substrate and found a high respiratory rate for the epithelium in both solutions. The stromal oxygen consumption was insignificant, in their opinion; the endothelial respiratory rate, which was zero in Ringer's solution, was revived in an aqueous medium. This observation substantiated Kohra's findings. They also reported a 60 to 80 per cent reduction of respiration in the presence of hydrogen cyanide.

Robbie, Leinfelder and Duane<sup>22</sup> (1947) applied the technic of controlled cyanide inhibition as perfected by Robbie<sup>23</sup> (1946) to the rabbit cornea in the Warburg apparatus. They found 50 per cent inhibition in concentrations of  $10^{-4}$  molar hydrogen cyanide and 93 per cent inhibition in solution of  $10^{-3}$  molar hydrogen cyanide. The remaining 7 per cent may have been associated with a non-metal-bearing, riboflavin-containing carrier. They demonstrated the labile linkage between the heavy metal and cyanide and stressed the importance of maintaining a constant hydrogen cyanide tension in this type of study. Furthermore, they showed that the cornea could be washed free of the cyanide and that the normal respiratory rate was resumed if glucose were present in the substrate. Robbie and his associates postulated that the cornea subsisted on glycolytic energy while under cyanide inhibition because they could demonstrate recovery when the cyanide was removed at the end of a five hour period only in those corneas which were in a glucose substrate; without glucose there was no

20. Hart, W. M., and Lee, O. S.: The Influence of Pontocaine, Cocaine, Procaine and Cyanide on the Uptake of Oxygen by the Cornea and the Effect of Added Substrate, *Proc. Am. Federation Clin. Research*, 1947, vol. 3.

21. Shesticova, T., and Rosenfeld, E.: The Respiration of the Cornea During Preservation, *Ukrainian Biochem. J.* 18:201, 1946.

22. Robbie, W. A.; Leinfelder, P. J., and Duane, T. D.: Cyanide Inhibition of Corneal Respiration, *Am. J. Ophth.* 30:1381, 1947.

23. Robbie, W. A.: The Quantitative Control of Cyanide in Manometric Experimentation, *J. Cell. & Comp. Physiol.* 27:181, 1946.

the dehydrogenation of lactic or malic acid or glycolysis, it was difficult to explain the inhibition of respiration and the accumulation of lactic acid in the tissues (as measured by the highly specific technic of Barker and Summerson,<sup>17</sup> 1941). Herrmann and associates assumed that the effect may have been on some carrier between lactic acid dehydrogenase and cytochrome oxidase. Possibly the drugs enhanced aerobic glycolysis (anaerobic glycolysis was not affected). They may have inhibited the resynthesis of lactic acid into dextrose; or perhaps, as suggested by these workers, the accumulation of lactic acid may have been a side reaction occurring in the respiring cornea.

Lee and Hart<sup>18</sup> (1944) determined that the oxygen consumption per hour for the whole rat cornea was 2.24 cu. mm., that for the epithelium 1.16 cu. mm. and that for the stroma 0.44 cu. mm. (table). They were unable to measure the endothelial respiration. The discrepancy between the sum of the stromal value and the epithelial value as compared with that for the intact cornea was interpreted by these authors as representing a result of the cellular trauma inherent in the mechanical removal of the epithelium from the cornea.

Both Orzalesi<sup>19</sup> (1939) and Lee and Hart<sup>18</sup> (1944) found the metabolic activity of the vitamin A-deficient (xerotic) cornea to be higher than normal. This was due to an increase in the epithelial respiration, since the stromal respiration did not change. Lee and Hart attributed the increased respiration to the metaplasia and hyperplasia of the epithelial cells. Orzalesi, who also noted an increase in the glycolytic activity of the xerotic cornea, concluded that the pronounced necrotic changes in the tissues might liberate substances capable of accelerating metabolism.

Lee and Hart<sup>18</sup> (1944) also investigated the respiration of the vascularized, riboflavin-deficient rat cornea and found the respiration in the later stages to be the same as that for normal controls. However, when the epithelium was measured alone, its oxygen consumption was markedly depressed. This depression occurred early in the deficiency; and when the respiration of the whole cornea was measured at this time it was found to be low, since no change in the stromal rate had occurred. Later, however, after parenchymal invasion of the blood vessels and cellular elements, the stromal respiration increased and thus accounted for the over-all normal values obtained from the intact corneas.

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17. Barker, S., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, *J. Biol. Chem.* **138**:535, 1941.

18. Lee, O. S., and Hart, W. M.: The Metabolism of the Cornea, *Am. J. Ophth.* **27**:488, 1944.

19. Orzalesi, F.: *Ricerche sulla glicolisi e respirazione della cornea di ratto albino in avitaminosa A*, *Boll. d'ocul.* **18**:442, 1939; *Zentralbl. f. d. ges. Ophth.* **44**:536, 1940.

epithelium. Thus the rate of glucose consumption in the stroma seemed to be under the control of the epithelium; i.e., there seemed to be an "intercellular Pasteur effect" operating in this tissue. The epithelial control was exerted through its supply of phosphates with high energy bonds. Mustard gas interfered with these processes, and the possible mechanisms of interference were discussed in detail. A special hydrogen transport mechanism for the epithelial utilization of stromal lactate, which did not operate in the endogenous consumption of epithelial lactate, was postulated. Lactate, pyruvate, serine and butyrate were not consumed by the stroma but were metabolized in the epithelium. Furthermore, glutathione and ascorbic acid were found in higher concentrations in the epithelium than in the stroma. These facts suggested that a complex boundary existed between the epithelium and the stroma and that expenditure of energy was necessary for the maintenance of the cohesive forces between these layers. Under Friedenwald's influence, and stimulated by his successes on similar interface boundary complexes, such as he found in the ciliary body, it was to be expected that this experimental team would search for analogous mechanisms in the stroma-epithelium boundary. The results have been less brilliant in this area, but the effects of known glycolytic enzyme inhibitors, such as mustard gas, iodoacetate and fluoride, on the loosening of the epithelium aerobically and anaerobically have at least suggested many theories and methods of approach, for which investigators in this field are deeply indebted to this group. The theories and hypotheses, as well as the results which accumulated during four years of secret research, are too extensive to be reviewed in detail in this article. The reader is referred to the original monograph. As Friedenwald stated in his final comment:

A series of unsupported hypotheses have been introduced chiefly centering around the assumption that the metabolic interaction may be located at the boundary of cohesion. There are very serious reasons for believing any such unifying theory is untrue, . . .

A more adequate evaluation of the theory may be made after the results have been confirmed in other laboratories.

Leinfelder<sup>27</sup> (1948) studied aerobic glycolysis in rabbit and bee corneas by the Summerson<sup>28</sup> (1939) technic. When the glucose concentration in the substrate was reduced to less than 0.2 mg. per cubic centimeter, glycolytic processes ceased, but they were restored when additional glucose was supplied. He also found a much higher rate of glycolysis in the epithelium than in the stroma. He compared

27. Leinfelder, P. J.: Glycolytic Activity of Corneal Tissue, to be published.

28. Summerson, W. H.: A Combination Simple Manometer and Constant Volume Differential Manometer for Studies in Metabolism, *J. Biol. Chem.* **131**:579, 1939.

recovery. Finally, the scraped cornea responded to cyanide inhibition like the whole cornea, showing the effect of hydrogen cyanide on the stroma. They found a mean oxygen consumption ( $QO_2$ ) of  $-0.46$  for the entire cornea and  $-0.15$  for the stroma. The epithelium was estimated to have an oxygen consumption of  $-6.0$  to  $-8.0$  (table 1). They stressed the adaptability of the cornea as a tool for tissue respiratory studies because it maintained a constant rate of respiration for more than six hours in a Ringer-phosphate solution.

Grant<sup>24</sup> (1947) studied the effects of the sulfur dioxide gas on the corneas of experimental animals after reviewing the effects of this compound on 4 human subjects whose corneas had been accidentally exposed to liquid sulfur dioxide. He found a complete inactivation of corneal catalase. He concluded that the toxic effect was due to sulfurous acid, which denatured the corneal proteins, including the enzymes.

Anderson<sup>25</sup> (1947) attempted, without success, to reproduce the corneal and conjunctival pigmentation found clinically in workers engaged in the manufacture of quinone and hydroquinone. He concluded that a specific intracellular oxidase necessary for the formation of a melanin-like substance might be missing in the experimental albino rabbits.

The February 1948 issue of the *Bulletin of the Johns Hopkins Hospital*<sup>26</sup> is devoted to experimental work performed at the Wilmer Institute during World War II on mustard gas burns (dichloroethyl sulfide) burns of the eye. The monograph describes in detail the various aspects of this problem as it was approached by the many workers in their laboratory group from 1941 to 1945. Over one-half the report contains descriptions, results and interpretations of Herrmann's experiments on the metabolic processes as they were influenced by mustard gas injury. This necessitated the investigation of many metabolic reactions in the normal control corneas in order to evaluate the changes produced by mustard gas.

They found a normal mode of glycolysis in the corneal epithelium under aerobic and anaerobic conditions. They stated that the stroma did not take up oxygen but that this layer was capable of utilizing glucose and of producing lactate, which could be utilized only by the

24. Grant, W. M.: Ocular Injury Due to Sulfur Dioxide: II. Experimental Study and Comparison with Ocular Effects of Freezing, *Arch. Ophth.* **38**:762 (Dec.) 1947.

25. Anderson, B.: Corneal and Conjunctival Pigmentation Among Workers Engaged in Manufacture of Hydroquinone, *Arch. Ophth.* **38**:812 (Dec.) 1947.

26. Staff of Wilmer Institute: Studies on the Physiology, Biochemistry and Cytopathology of the Cornea in Relation to Injury by Mustard Gas and Allied Toxic Agents, *Bull. Johns Hopkins Hosp.* **82**:81, 1948.

either of which was sufficient to maintain transparency and viability. Laquer<sup>31</sup> (1872) and Gruber<sup>30</sup> (1894) produced further evidence for this hypothesis from the observations that rust spots in the cornea became blue after injection of potassium ferricyanide into the blood stream or into the anterior chamber.

Weekers<sup>11</sup> (1940), in a review article, discussed the contradictory results of various workers on the permeability of the cornea with regard to oxygen, carbon dioxide and mineral salts. He lamented the gaps in the knowledge of the metabolism of the cornea and stated that it was difficult, if not impossible, to trace a coherent scheme of chemical changes taking place in this tissue. Parenthetically, one should note that this ignorance extends to most tissues. Since the normal temperature of the cornea is less than that of the iris (Duke-Elder,<sup>32</sup> 1927), it is probable that the metabolism of the cornea is correspondingly less. Weekers discussed the three theoretic sources of substrate for corneal metabolism—the aqueous, the tears and the limbal capillaries. Leber<sup>33</sup> (1903), without experimental evidence, attributed the main role to the limbal capillaries, which supposedly satisfied the periphery of the cornea but left the center in a precarious position.<sup>34</sup> Wessley<sup>35</sup> (1905), while not denying the role of the limbal capillaries, stated the opinion that the chief energy for corneal metabolism stemmed from the aqueous. Terry<sup>36</sup> (1939) recognized three sources of nutritive substances, and Rollet<sup>37</sup> (1936) attached main importance to the tears. Weekers concluded that in reality the findings were too incomplete to permit any formal conclusions, but suggested that the substances most directly utilized in the metabolism of the cornea were oxygen and glucose.

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31. Laquer, L.: Ueber die Durchgängigkeit der Hornhaut für Flüssigkeiten, *Centralbl. f. d. med. Wissensch.* **10**:577, 1872.

32. Duke-Elder, W. S.: Nature of the Intraocular Fluid, *Brit. J. Ophth.*, monograph supp. III, 1927.

33. Leber, T., in Graefe, A., and Saemisch, T.: *Handbuch der gesamten Augenheilkunde*, ed. 2, Leipzig, W. Englemann, 1903, vol. 2, p. 355.

34. This particular point of view was supported by the experiments of Cogan and Kinsey (The Cornea: V. Physiologic Aspects, *Arch. Ophth.* **28**:661 [Oct.] 1942), though they differed notably from Leber in the interpretation of other physiologic properties of the cornea, the role of the endothelium, for example. (The reviewer has attempted to determine whether there was a gradient of respiration from periphery to center in the bovine and rabbit total cornea and has obtained inconclusive results, owing to the low oxygen consumption of these tissues.)

35. Wessley, K.: Der Flüssigkeits-und Stoffwechsel des Auges mit besonderer Berücksichtigung seiner Beziehungen zu allgemeinphysiologischen und biologischen Fragen, *Ergebn. d. Physiol.* **4**:565, 1905.

36. Terry, T.: Some Physiological and Anatomical Aspects of the Cornea Affecting Its Pathology, *Am. J. Ophth.* **22**:153, 1939.

37. Rollet, J.: La couche de liquide pré-cornéene, *Arch. d'opht.* **53**:111 and 255, 1936.

the glycolytic activity of the fresh and that of the stored cornea and concluded that when the cornea was stored without available glucose there might have been a shift in the  $p_H$  of the tissue toward the alkaline side.

*Comment.*—With the evolution of more sensitive technics, experimenters have come to agree on certain aspects of corneal respiration. All workers agree that the epithelium respire a certain amount, but there is some question about the stroma and the endothelium. The value of the individual oxygen consumption for a given tissue layer in a given species remains unsettled. The effects of certain anesthetic drugs have been corroborated by at least two groups, although the effect of cocaine on corneal respiration is debated. Evidence has been presented to show that a heavy metal system, probably cytochrome-cytochrome oxidase, is directly involved in the respiratory events in the cornea. Furthermore, the cornea is capable of carrying on aerobic and anaerobic glycolysis and, indeed, may depend on the latter under low oxygen tensions. The exact role of riboflavin, i.e., whether it acts as an autoxidizable substance or whether it behaves as a flavoprotein link between the dehydrogenases and the cytochrome systems, is still unsolved. The practical value of an answer to the question becomes apparent when it is recalled that corneal vascularization accompanies riboflavin deficiency, probably because of a need for increased supply of oxygen to the corneal epithelium. There is evidence that the cohesive attraction of epithelium to stroma is under the control of forces which are enzymatically generated near the boundary and that these forces can be altered with glycolytic enzyme inhibitors, including mustard gas. The changes which occur in the stored cornea have been investigated, and it is possible that longer periods of preservation in eye banks may result from study of these phenomena. Finally, quite aside from the practical application to ophthalmology, the recent studies on corneal respiration have proved that this organ is an enduring and valuable material for laboratory investigations.

#### THE FLUID ENVIRONMENT OF THE CORNEA

Coccius<sup>29</sup> (1852) noted that the cornea remained viable when the anterior chamber was filled with air, and Gruber<sup>30</sup> (1894) reported that the cornea remained transparent after a complete peritomy. Hence, from these early years, it was believed that the cornea had a dual source of nourishment from the pericorneal vessels and from the aqueous,

29. Coccius, E. A.: Ueber die Ernährungsweise der Hornhaut und die Serum-führenden Gefässe in menschlichen Körper, I. Müller, Leipzig, 1852.

30. Gruber, R.: Beiträge zur Kenntniss der Hornhaut Circulation, Arch. f. Ophth. 40:25, 1894.

This statement, made by Alan Woods in his provocative presidential address before the American Academy of Ophthalmology and Otolaryngology, suggests the challenge to investigators in this area.

#### SUMMARY

The literature on the respiratory activity of the cornea is reviewed with respect to several aspects. The relation of corneal respiration to the atmospheric environment is analyzed. The respiratory rates of the various corneal strata are collected, evaluated and recorded in tabular form. Evidence for the presence and operation of the various respiratory enzyme systems is discussed. Finally, the possible sources of nutrition for the cornea are reviewed.

Medical Laboratories.



The presence of sugar in the tears was admitted by some authors and denied by others (Terry<sup>38</sup> [1939]; Ridley<sup>38</sup> [1930]; Michail, Vanca and Zolog<sup>39</sup> [1937]). By contrast, the presence of the reducing substance in the aqueous could not be denied, and it was plausible to admit that an important part of the reducing power could be attributed to glucose. But as Kinsey<sup>40</sup> has suggested, one must realize that ascorbic acid, which is present in the aqueous,<sup>41</sup> might also account for the reductions. It was impossible to estimate the importance of glucose in the capillary system. The tears, aqueous and blood could all furnish oxygen to the cornea. By virtue of its situation, the cornea was better able to metabolize aerobically than the lens. Weekers also cited the work of Bullo<sup>42</sup>. Whether the metabolic exchanges occur in the epithelium, endothelium or parenchyma was, he thought, a moot question. He stated that "at the most it can be noted that certain substances, not elements of the structure, are found in the cornea—perhaps products of diffusion, possibly metabolic substrates and by-products—such substances as malic acid, creatine, citric acid (Krause and Stack<sup>43</sup>), formic acid (Krause and Weekers<sup>43</sup>) and inositol (Krause and Weekers<sup>44</sup>)."  
 Weekers concluded that with more research the etiology of keratitis will unfold and the number of successful corneal grafts will increase.

#### FINAL COMMENT

There are many conflicting opinions about the various factors which influence the respiration of the cornea, but one thing is clear:

It is impossible for us to understand or properly treat the degenerative diseases of the cornea until we have a sound knowledge of the corneal metabolism and the changes therein wrought by injury and disease.<sup>45</sup>

38. Ridley, F.: The Intraocular Pressure and Drainage of the Aqueous Humor, *Brit. J. Exper. Path.* **11**:217 (1930).
39. Michail, D.; Vanca, P., and Zolog. C. R.: Sur l'élimination lacrymale du glucose chez les diabétiques, *Compt. rend. Soc. de biol.* **125**:194, 1937.
40. Kinsey, V. E.: Personal communication to the author.
41. Friedenwald, J. S.; Buschke, W., and Michel, H. O.: Role of Ascorbic Acid (Vitamin C) in Secretion of Intraocular Fluid, *Arch. Ophthalm.* **29**:535 (April) 1943.
42. Kinsey, V. E.; Jackson, B., and Terry, T. L.: Development of Secretory Function of the Ciliary Body in the Rabbit Eye, *ibid.* **34**:415 (Nov.-Dec.) 1945.
43. Kinsey, V. E.: Transfer of Ascorbic Acid and Related Compound Across the Blood Aqueous Barrier, *Am. J. Ophthalm.* **30**:1262, 1947.
44. Krause, A. C., and Stack, A. M.: Citric and Malic Acids of the Ocular Tissues, *Arch. Ophthalm.* **22**:66 (July) 1939.
45. Krause, A. C., and Weekers, R.: L'acide formique des tissus oculaires, *Arch. d'opht.* **3**:225, 1939.
46. Krause, A. C., and Weekers, R.: Inositol in Ocular Tissues, *Arch. Ophthalm.* **20**:299 (Aug.) 1938.
47. Woods, A. C.: The Present Policies of the American Board of Ophthalmology and the National Societies in Relation to the Progress of Ophthalmology, *Tr. Am. Acad. Ophthalm.* **52**:5, 1947.

and treasurer. The scientific program was enjoyed by sixty-five ophthalmologists, from Ohio, Indiana, Illinois, Wisconsin, Minnesota, Iowa, Nebraska, Kansas and Missouri.

Papers covering a wide range of scientific research in ophthalmology were presented.

**Association for the Prevention of Blindness (Mexico).**—The medical staff of the Mexican Association for the Prevention of Blindness announces its annual meeting, to take place from November 6 to 13, 1949, at the Association Hospital, México, D. F., Mexico.

Papers to be presented must be sent to the association not later than Oct. 1, 1949, and must take not more than fifteen minutes in reading time and presentation of slides.

The fee for inscription at the meeting is 50 pesos (Mexican).

**Western Section of the Association for Research in Ophthalmology.**—The section's annual meeting was held on March 25, 1949 at the University of California Medical School. A scientific program of general interest was presented, followed by a general meeting, at which "Aspects and Activities of the Central Nervous System" was discussed by Prof. John B. DeC. M. Saunders, F.R.C.S., professor of anatomy and lecturer in medical history at the University of California Medical School.

**Alabama Academy of Ophthalmology and Otolaryngology.**—The Alabama Academy of Ophthalmology and Otolaryngology announced its formation on April 20, 1949. The following officers were elected: Chairman, Dr. Frank Clements, of Birmingham; chairman elect, Dr. Phil P. Gilchrist, of Mobile; secretary-treasurer, Dr. Karl B. Benkwith, of Montgomery. Committees on credentials and by-laws are now being appointed by the chairman.

# News and Notes

EDITED BY DR. W. L. BENEDICT

## GENERAL NEWS

**Oregon Academy Postgraduate Convention in Ophthalmology and Otolaryngology.**—The Oregon Academy of Ophthalmology and Otolaryngology has announced its tenth annual spring convention, to be held from June 19 to June 24, 1949.

The guest speakers will be: Dr. Lawrence R. Boies, professor of otolaryngology, University of Minnesota Medical School, who will discuss chronic conditions of the ear and nose and current problems in otolaryngology; Dr. Leland Hunnicutt, associate clinical professor of otolaryngology, University of Southern California School of Medicine, who will speak on hemorrhagic problems in the ear, nose and throat, and Dr. Edmund B. Spaeth, professor of ophthalmology, University of Pennsylvania School of Medicine, who will discuss surgery of the eye. Round table luncheon discussions will be held daily. Fee for the postgraduate convention is \$75, which includes the cost of daily luncheons.

**Royal Australasian College of Surgeons.**—The twenty-second annual general meeting of the Royal Australasian College of Surgeons will be held in Brisbane, June 7 to 10, 1949. A preliminary program of the meeting includes, for the section of laryngo-otology, papers on sinusitis in children, tumors of the pituitary gland, bilateral abductor laryngeal paralysis, control of vertigo and the fenestration operation. In the section for ophthalmology, lectures will be given on aspects of the treatment of intraocular tumors, orbital tumors, surgery of the inferior oblique muscle, dacryocystorhinostomy and pathology of the eye. Dr. H. G. Wheeler, of Melbourne, is secretary of the College.

**Postgraduate Lectures, University of Glasgow.**—The University of Glasgow, Department of Ophthalmology, has announced a series of postgraduate lectures to be given in May 1949. The lectures are scheduled as follows:

May 4: "European Vacation," Prof. W. J. B. Riddell; May 11: "Pupillary Movements," Dr. Forgas Campbell; May 18: "Structure of the Vitreous Humour," Dr. Antoinette Pirie; May 25: "Bleeding and Clotting Within the Eye," Dr. W. O. G. Taylor.

## SOCIETY NEWS

**Midwestern Section of the Association for Research in Ophthalmology.**—The Midwestern Section of the Association for Research in Ophthalmology held its organizational meeting in the Elliott Auditorium, Oscar Johnson Institute, St. Louis, on Saturday, March 26, 1949. William F. Hughes Jr., M.D., was elected chairman; William Howard Morrison, M.D., vice chairman, and T. E. Sanders, M.D., secretary



JOHN ELMER WEEKS  
1853-1949

# Obituaries

## JOHN ELMER WEEKS, M.D.

1853-1949

Dr. John Elmer Weeks was born in Painesville, Ohio, Aug. 9, 1853, the son of Seth and Deborah Blydenburgh Weeks, and died in La Jolla, Calif., Feb. 3, 1949. After a preliminary education in the schools of Painesville, and in Corry, Pa., he graduated in medicine from the University of Michigan, in 1881, and engaged in general practice in Corry, Pa., and Hamlet, N. Y., until Feb. 1, 1882.

He was an intern of the Work House Hospital, New York, from April 1, 1882 to April 1, 1883, and resident physician at the New York Emigrant Hospital from April 1, 1883 to April 1, 1885.

Dr. Weeks began his training in ophthalmology under Dr. Herman Knapp at the New York Ophthalmic and Aural Institute. He first attended the outpatient department in 1883 and then acted as resident from 1884 to 1886. It was in the laboratory of this hospital that Dr. Weeks, in 1886, investigated acute contagious epidemic conjunctivitis ("pink eye") and discovered the causative organism, which has become known as the Koch-Weeks bacillus (Weeks, J. E.: The Bacillus of Acute Conjunctival Catarrh, or Pink Eye, *Arch Ophth.* 25: 441-451, 1886). Dr. Weeks acted as assistant surgeon and instructor in this institution from 1887 to 1889, as well as chief of the clinic in the department of ophthalmology in the New York University Medical College from 1886 to 1888, and occupied a similar position at the College of Physicians and Surgeons, New York, from 1888 to 1890. He then became lecturer on ophthalmology in Bellevue Hospital Medical College in 1890 and professor of ophthalmology in 1900, until he was appointed emeritus professor in 1921. He was one of the surgeons of the New York Eye and Ear Infirmary from 1890 to 1920. He developed the laboratory of pathology and bacteriology at the Infirmary and, together with Dr. George A. Dixon, devised a method of roentgenologic localization of intraocular foreign bodies.

Dr. Weeks was the author of a well known textbook (A Treatise on Diseases of the Eye, Philadelphia, Lea & Febiger, 1910) and contributed many articles to ophthalmologic publications, usually on clinical and operative subjects; one of the latter was on a method of restoration of the orbital socket.

He was chairman of the Section on Ophthalmology of the American Medical Association in 1905, chairman of the Section of Ophthalmology of the New York Academy of Medicine, president of the American

# Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

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## Cornea and Sclera

PENICILLIN IN INTERSTITIAL KERATITIS. J. V. KLAUDER, *Am. J. Syph., Gonorr. & Ven. Dis.* 31: 575 (Nov.) 1947.

Seventy-two patients, 22 male and 50 females between the ages of 5½ and 46 years, with interstitial keratitis were treated with penicillin. Sufficient time has elapsed to evaluate the results of treatment in 59 of these patients. Forty-one of the 59 patients were given intramuscular injections of 50,000 units of commercial sodium penicillin every four hours for forty-eight consecutive doses in eight days, to a total amount of 2,400,000 units. For the remaining 18 patients the total dose of penicillin ranged from about 500,000 (2 patients) to about 4,000,000 units. The majority received about 2,000,000 units in eight days. Penicillin was well tolerated, without serious untoward reactions. The Herxheimer reaction was absent after initial treatment. Twenty-five patients were given penicillin alone. Nine patients received penicillin combined with eight to twelve inductions of fever with vaccines; 21 patients, penicillin, fever therapy and chemotherapy; 4 patients, penicillin and chemotherapy. In the 25 patients treated with penicillin only, interstitial keratitis progressed favorably or was retrogressing at the time penicillin was given, so that supplemental treatment was not regarded as necessary. Penicillin, like chemotherapy, did not prevent an initial attack of interstitial keratitis, involvement of the second eye or recurrence of the disease in the previously affected eye. The absence of any striking result in the final visual acuity of the penicillin-treated patients is consistent with clinical observation that penicillin does not uniformly exert an immediate favorable effect on active interstitial keratitis. The considerable individual variation in the course of this disease is apparently not altered by penicillin therapy. Interstitial keratitis which was retrogressing at the time of treatment pursued a favorable course, as did mild forms of the disease. An occasional patient with a severe form of the disease seemed to be benefited; such other patients were definitely not improved by penicillin or any other method of treatment. Retreatment with penicillin in refractory cases did not seem to be of benefit. There was no apparent effect after the local use of penicillin. The addition of penicillin to the therapeutic agents for interstitial keratitis does not give results superior to those of other forms of treatment.

J. A. M. A. (W. ZENTMAYER.)

Ophthalmological Society in 1921; president of the New York County Medical Society, and a member of the New York Ophthalmological Society, the Academy of Ophthalmology and Oto-Laryngology, the Ophthalmological Society of the United Kingdom and the Royal Hungarian Medical Society.

He established a scholarship for research work in ophthalmology in the University of Michigan Medical School in 1921, and this college, his alma mater, conferred on him the honorary degree of Doctor of Science in 1934. He received the degree of Doctor of Laws from the New York University and Bellevue Hospital Medical College, and the University of Oregon Medical School elected him honorary professor of ophthalmology.

Dr. Weeks was a man of singular determination and industry, and an unusually dextrous operator, with sound judgment; his quiet self assurance and an infinite capacity for work made him the successful practitioner that he was during the thirty-eight years that he practiced in New York. His opinion and advice were greatly valued by his fellow practitioners, and were particularly in demand at the meetings and discussions which took place. In 1925 he retired from practice in New York city and moved to Oregon.

While continuing his professional work in Portland, Dr. Weeks took great interest in the University of Oregon Medical School and in 1939 donated the necessary funds for a library and auditorium, which are regarded as among the finest in the country. He found congenial opportunity in assisting with advice and financial support in the development of the department of ophthalmology, which was started in 1944 by Dr. Kenneth C. Swan, and one of his donations permitted the foundation of a clinic for binocular vision. The establishment of an ophthalmologic laboratory in this medical school, Dr. Swan writes, was of particular interest to Dr. Weeks, and he frequently compared it to his establishing the laboratory at the New York Eye and Ear Infirmary in 1890. The laboratory in Portland is now completely equipped, and, with its excellent museum, will shortly be moved to larger quarters and will be named in memory of Dr. Weeks.

Dr. Weeks lived long, but never grew old, and to the end retained an ardor and alertness that were envied by all; his modesty, his unfailing equanimity and his superb courage were remarkable. When asked, after he had retired, where he would advise a young ophthalmologist to settle, he replied, "Wherever the competition is the keenest."

He married Miss Jennie Post Parker in 1890; she was his devoted companion and helpmate for the many years of his life and made possible a family life which was singularly happy. Their daughter married Dr. F. R. Mount of Portland, Ore.

ARNOLD KNAPP.

These lesions do not disrupt the corneal lamellas, are not liable to secondary infection and cause little inflammatory reaction. After the lesions have healed, the cornea is clear.

W. S. REESE.

TISSUE RESEARCH AND CELL CULTURE OF THE CORNEA. D. HOOF, *Am. J. Ophth.* 31:709 (June) 1948.

Hoof believes that her preliminary experiments in tissue culture show the possibility of growth of the parenchyma cells out of the substantia propria. Her results would seem to substantiate the theory that the corneal graft lives as an independent tissue within the host's cornea, as advanced by Marchand, Fuchs, Filatov, Castroviejo, Leoz, Ortin, Ascher, Sommer and others.

W. S. REESE.

### General Diseases

MIKULICZ'S DISEASE AND SYNDROME. P. HEATH, *Am. J. Ophth.* 31:955 (Aug.) 1948.

Heath reports a case of "pure" Mikulicz disease and several cases of enlargements of lacrimal glands due to tuberculosis, sarcoid, gout, syphilis and giant follicular hyperplasia. He discusses the differential diagnosis and states the belief that so-called Mikulicz' disease is probably a granulomatous response of lymphatic tissue of the reticulo-endothelial system to a stimulus.

W. S. REESE.

XERODERMA PIGMENTOSUM WITH AFFECTION OF THE EYE. J. SÆBØ, *Brit. J. Ophth.* 32:398 (July) 1948.

After a brief description of xeroderma pigmentosum and melanoma in general, Sæbø reports 3 cases in which the eye was involved. In the first case a pterygium-like tumor developed at the age of 15, and lentigenes were present on the skin. The tumor was excised at the age of 17. New growths of the skin which proved microscopically to be malignant were constantly reappearing. The second case was that of a brother of the first patient. He had a history of the presence of brown spots on the face, neck and extremities for many years. At the age of 27 a tumor developed on the neck. In the right eye a vascular spot appeared on the conjunctiva. The familial incidence suggested that the disease was hereditary and was in all probability due to a recessive gene. In a third case of xeroderma pigmentosum a small, whitish tumor of the corneal limbus of the left eye appeared at the age of 10 years. Eight years later the tumor had infiltrated the entire cornea and part of the sclera. The right eye became similarly affected. Both eyes were blind at the age of 20 years and were enucleated. The new growths spread over the entire face, and death occurred one year later.

The author stresses the importance of keeping this disease in mind, even in cases of a seemingly benign tumor in the eye when it appears in conjunction with pigmented spots in the skin. Finally, mention is made of the eugenic measures that should be taken in order to prevent the spread of this serious, hereditary disease.

W. ZENTMAYER.



ON RESULTS OBTAINED BY TOTAL CONJUNCTIVAL HOODING OF THE CORNEA FOR SERPIGINOUS ULCER. A. KETTESY, *Brit. J. Ophth.* 32: 36 (Jan.) 1948.

The procedure consists in covering the whole cornea by a conjunctival flap. The operation is described in detail. Against the objections which have been raised to this method can be set the saving of an eye, or, rather, the saving of vision that would have been lost by any other treatment, and the duration of medical attendance expressed in days of hospitalization.

The average stay in the hospital was four days, and a later stay of three days when the patient returned for removal of the hood, at least six months after the operation. Tables are given showing that in a series of 56 patients treated conservatively, vision was improved in 26, worse in 4 and unchanged in 26, whereas in a series of 56 patients treated by hooding, vision was improved in 45, worse in 1 and unchanged in 10.

Total conjunctival hooding of the cornea is being increasingly employed by Kettesy for keratitic processes.

W. ZENTMAYER.

INTERSTITIAL KERATITIS AND PENICILLIN. I. VOISIN, *Bull. Soc. d'ophth. de Paris*, February 1948, p. 47.

In the case reported, interstitial keratitis had existed in one eye for some time and had appeared in the other eye at the time of the treatment with penicillin, which was given locally, by subconjunctival injection and, generally, by intramuscular injection. The author was impressed with the fact that subconjunctival injection was apparently most efficacious in the acutely inflamed eye. He raises the question whether the penicillin acts as a bacteriostatic or as an antiallergic agent.

L. L. MAYER.

A CASE OF NODULAR RHEUMATIC EPISCLERITIS. C. EDSTROM and G. OSTERLUND, *Acta ophth.* 26: 1, 1948.

A man with chronic rheumatic polyarthritis exhibited episcleral nodules in each eye. Histologic examination of these nodules showed that specific rheumatic tissue changes were present. Material from an excised nodule failed to grow on Loewenstein's substrate and produced no tuberculous changes on being injected into a guinea pig. At autopsy, rheumatic granulomas of the Aschoff type were demonstrable in the myocardium.

O. P. PERKINS.

### Experimental Pathology

REGENERATION OF THE CORNEAL STROMAL CELLS: I. TECHNIQUE FOR DESTRUCTION OF CORNEAL CORPUSCLES BY APPLICATION OF SOLIDIFIED (FROZEN) CARBON DIOXIDE. A. E. MAUMENEE and W. KORNBLUETH, *Am. J. Ophth.* 31: 699 (June) 1948.

Maumenee and Kornblueth found that freezing various-sized areas of the cornea to  $-78^{\circ}\text{C}$ . for three to five seconds produces a convenient lesion for the study of regeneration of the cells of the corneal stroma.

sure, since the intraocular pressure varies as the capillary pressure. The author believes that whenever these tests are positive their effect is exerted through the hypothalamic centers.

The results of the tests depend on the state of the diencephalon at the time the test is performed. It must be remembered that an increase in tension is only one of the signs of glaucoma and that the disease may be present despite a normal or subnormal tension.

P. R. McDONALD.

A FAILING DOGMA: OCULAR HYPERTENSION IN GLAUCOMA. M. MARQUEZ, *Ann. d'ocul.* 181:351 (June) 1948.

The author reviews his personal observations on glaucoma and the concepts that have been advanced concerning the etiology of the disease. In the great majority of cases too great importance has been attached to the ocular hypertension. In cases of acute glaucoma the tension is the predominant feature, whereas in cases of chronic simple glaucoma the cupping of the nerve head and changes in the fields are most apparent.

It is evident that in the majority of cases of glaucoma the signs and symptoms of glaucoma and ocular hypertension occur together. There are some cases of glaucoma without hypertension and cases of hypertension without glaucoma. In general, there are two types of glaucoma: the anterior type, which affects the ciliary body and is usually acute, and the posterior type, which affects the nerve and the retina and is usually chronic, and not necessarily accompanied with hypertension. In the latter category may fall cases of cavernous atrophy without field changes or field changes without atrophy.

The present consensus is that ocular tension is not the only factor in glaucoma. In many cases the tension is promptly reduced by operation but the visual defects continue unabated.

It is not enough to treat glaucoma by attempting to reduce the intraocular pressure. One should try to treat the capillaries of the optic nerve. Vasodilator substances or rutin may be tried. The author is of the opinion that in chronic simple glaucoma hypertension is not the cause, but only one of the symptoms.

P. R. McDONALD.

### Injuries

TRAUMATIC CYSTS OF THE IRIS DUE TO EPITHELIAL IMPLANTATION. J. A. GALLINO and A. BENJAMIN, *Arch. de oftal. de Buenos Aires* 22:124 (April-June) 1947.

The appearance of cysts in the anterior chamber and stroma of the iris represents one of the least frequent sequelae of perforating traumas of the eye, especially of those which denote a certain amount of violence, such as that in the authors' case. They express the belief that the history in this case entirely confirms the theory of migration and implantation of the corneal epithelium, in view of the large number of cysts of every size which were found implanted in the iris and free in the anterior chamber.

M. E. ALVARO.

## Glaucoma

MILD GLAUCOMA. ADOLPH POSNER and A. SCHLOSSMAN, *Am. J. Ophth.* 31: 679 (June) 1948.

Posner and Schlossman remark the mildness of glaucoma in certain cases, in which the fundi, fields and central vision remain unaltered for years. They report 17 of a total of 40 such cases in a series of 373 cases of glaucoma. They suggest that the severity of the disease be determined before miotic therapy is instituted.

W. S. REESE.

INTRAOCULAR PRESSURE OF NORMAL AND GLAUCOMATOUS EYES AS AFFECTED BY ACCESSORY LIGHT STIMULI. R. B. ZARETSKAYA, *Am. J. Ophth.* 31: 721 (June) 1948.

Zaretskaya studied fluctuations in the intraocular pressure due to light stimuli, especially white or colored light, on the second eye. He suggests that, since green light causes a decided drop in intraocular pressure in glaucomatous patients, advantage might be taken of this therapeutically by use of green spectacles.

W. S. REESE.

PROVOCATIVE TESTS AND GLAUCOMA. A. MAGITOT, *Ann. d'ocul.* 181: 338 (June) 1948.

The author decries the idea held by many ophthalmologists that increased tension and glaucoma are synonymous.

In many instances, early in the disease the periods of increased tension are transitory. A provocative test would be of great value in diagnosis of incipient glaucoma and of the so-called soft glaucoma. The use of a mydriatic, such as atropine, is not an acceptable method. If the drug produces an acute attack, it is difficult to counteract its effect. The results are also uncertain, since in some cases of glaucoma the tension is not elevated, and it may even be lowered.

Seidel was the first to suggest the darkness test. The subject is kept in darkness for thirty to sixty minutes, and the glaucomatous subject may show an appreciable rise in tension. The author does not believe that the rise in tension is dependent on dilatation of the pupil and embarrassment of the angle. He feels that it is due directly to the action of light on the hypophysis. The result is negative if the diencephalon is not in a stage of excitability.

Another provocative test is the massage or compression of the eyeball. There is first a drop in tension and then a secondary rise. The results are not always reproducible, however.

The use of caffeine, likewise, is not reliable and when tried on known glaucomatous subjects may not cause a rise in tension.

The raising of the venous pressure and the lability test of Schoenberg and Bloomfield are discussed in detail. The author feels that immersion of the hands in cold water may raise the intraocular tension through the thalamic centers and that the vascular response to cold is not significant. He cites the fact that ligation of the jugular veins does not cause an increase in intraocular tension.

In conclusion, the water-drinking test of Schmidt is discussed. This, like most of the other tests, is an attempt to disturb the capillary pres-

cation previously described was a transitory paresis of the ocular muscles. The author has seen persistent changes in the pupillary reactions following the procedure. These changes have led to interesting speculation concerning the pathogenesis of Adie's syndrome.

The pupillary changes were noted in 4 patients, 3 men and 1 woman. These alterations did not follow an excessive injection of alcohol. Three stages were noted in the pupillary disturbances: 1. The pupil was dilated and did not react to light or in accommodation. This stage lasted several weeks. 2. The pupil was dilated and did not react to light. The reactions in accommodation and convergence were present, and recovery was very slow. In this stage the pupillary reaction simulated Adie's syndrome. In time the third stage was noticed. 3. The pupil was dilated and appeared to be fixed to light; however, with the slit lamp a faint response to light was noted. The accommodation-convergence reaction was still tonic. This stage may remain for years.

In attempting to explain the pharmacodynamics of this pupillary abnormality, the effects of several drugs were investigated. The affected eyes were shown to be sensitive to methacholine, as first demonstrated by Adler and Scheie. The author believes that the tonic pupil following the retrobulbar injection of alcohol is produced by a lesion of the iridoconstrictor (parasympathetic) fibers in the orbit.

P. R. McDONALD.

### Retina and Optic Nerve

THE PRESENT STATE OF THE PROBLEM OF RETINITIS PIGMENTOSA.

I. BIRO', Brit. J. Ophth. 32: 411 (July) 1948.

It is evident that typical retinitis pigmentosa, in the majority of cases, is not an independent ophthalmic disease but a manifestation of a widely branching complex, the nucleus of which is the pathologically altered functions of the pituitary and the diencephalon and the hormonal consequences thereof.

The author emphasizes the dual pathogenesis of the disease, as described by Redslob, namely, (1) inherited, and (2) "*sui generis*," or "autonomous." The inherited type is further divided into the recessive type and that inherited as a dominant.

In contradistinction to the hereditary form, the autonomous form is a sequel of such diseases as the acute exanthems, inflammations, toxic diseases and permanent circulatory impairment; and the hereditary and autonomous forms have certain clinical differences. The autonomous form is not without the possibility of permanent improvement, but no treatment can be expected to influence the inherited disease.

W. ZENTMAYER.

PROGNOSIS OF RETROBULBAR NEURITIS. W. F. T. TATLOW, Brit. J. Ophth. 32: 488 (Aug.) 1948.

The purpose of the investigation was to discover in how many cases of retrobulbar neuritis disseminated sclerosis eventually developed, after a number of years. Tatlow summarizes his study as follows: The

## Ocular Muscles

ANATOMIC FACTORS IN THE ETIOLOGY OF HETEROTROPIA. RICHARD G. SCOBEE, *Am. J. Ophth.* 31:781 (July) 1948.

Scobee discusses the anatomic factors which he believes are responsible for 90 per cent of all cases of heterotropia appearing in the first six years of life. He classifies the causes of heterotropia as follows: (1) anatomic: (a) abnormal origins of muscles, (b) abnormal insertions, (c) abnormal muscle slips, (d) abnormal check ligaments, (e) abiotrophies; (2) innervational: (a) nervous (anomalies of convergence and divergence), (b) refractive (accommodative), (c) amblyopic (any organic obstacle to fusion); (3) paretic: (a) toxic, (b) traumatic, (c) congenital.

W. S. REESE.

A TECHNIQUE FOR MUSCLE RESECTION WITHOUT THE USE OF THE PRINCE FORCEPS. E. YASUNA, *Am. J. Ophth.* 31:972 (Aug.) 1948.

Yasuna describes a simple technic for muscle resection in which a double-armed suture is placed near the insertion of the muscle and then beyond it and the intervening tendon resected, ordinary forceps being used instead of the Prince forceps, which he considers unsafe.

W. S. REESE.

## Operations

FURTHER EXPERIENCES WITH INTEGRATED EYES AND VITALLIUM IMPLANTS. W. L. HUGHES, *Am. J. Ophth.* 31:854 (July) 1948.

Hughes describes an operation in which he uses a vitallium® implant with an aperture to provide for fixation of an artificial eye. He makes a preliminary report on 5 cases.

W. S. REESE.

OCULAR SURGERY. FELICIANO PALOMINA DENA, *An. Soc. mex. de oftal. y oto-rino-laring.* 21:88 (April-June) 1947.

Palomina Dena states that corneal grafting and the technic of keratotomy have progressed until they are now perfected and give satisfactory results. The intracapsular cataract operation offers the greatest security. In the present treatment of retinal detachment localization of a tear is unnecessary. Strabismus is no longer fundamentally a surgical problem. Glaucoma continues to be the chief problem in ophthalmology, and until the etiologic and pathogenic factors are determined, surgical treatment will be symptomatic, and the disease will remain as an important cause of blindness.

M. E. ALVARO.

## The Pupil

TONIC PUPIL PRODUCED BY THE RETROBULBAR INJECTION OF ALCOHOL. R. WEEKERS, *Ann. d'ocul.* 181:193 (April) 1948.

The retrobulbar injection of alcohol is an accepted method of treating pain in the eyeball. The injection of 1.5 cc. of a 40 to 50 per cent alcohol has no effect on the retina or the optic nerve. The only compli-

## Tumors

A MYXO-HAEMANGIOMA SIMPLEX OF THE CONJUNCTIVA BULBI. A. BAKKER, Brit. J. Ophth. 32: 485 (Aug.) 1948.

A rapidly growing, finger-like tumor with a broad, short pedicle was removed from the bulbar conjunctiva of the right eye in a woman aged 35. The tumor had a cherry red color and a smooth surface and was surrounded by a thin fibrous capsule. The diagnosis was hemangioma simplex of the conjunctiva bulbi with signs of intensive proliferation and myxomatous degeneration.

W. ZENTMAYER.

INDICATIONS FOR CONTACT RADIOTHERAPY IN TREATMENT OF TUMORS OF THE LIDS. F. BACLESSE and A. ENNUYER, Arch. d'opht. 7: 5, 1947.

The authors report a review of 200 cases. They first describe the procedure involved with the use of a contact radiotherapy machine designed by Philips. A number of photographs, showing conditions before and after treatment, accompany the article. The tumors for which this treatment is indicated are many. Epitheliomas and angiomas of the lids are the most frequent. The method is also of equal value in the treatment of epitheliomas of the cornea. In the authors' experience, no late ocular damage has been observed. The technic constitutes the best protection for the eye. It also allows the ambulatory treatment of a large number of patients.

S. B. MARLOW.

SYMPATHICOBLASTOMAS WITH METASTASES TO THE ORBIT. H. OLESEN and F. SJØNTØFT, Acta ophth. 26: 67, 1948.

The authors give a lucid description of the genesis, pathologic characteristics and symptoms of sympathicoblastomas. They stress the difficulty of differential diagnosis, particularly from chloroma. Two cases are reported, with photomicrographs of the tumor.

O. P. PERKINS.

## Uvea

CONTRIBUTION TO DATA ON SIGHT DISTURBANCES CAUSED BY PROLIFERATION OF PIGMENT EPITHELIUM. M. RADNÓT, Brit. J. Ophth. 32: 423 (July) 1948.

Radnót states that serious disturbance may be caused by proliferation of the pigment epithelium of the iris in the case of after-cataract resulting from the deposit of pigment on the surface of the remaining capsule. The author describes the case of a woman aged 83 in whom, after an intracapsular extraction with a round pupil, the surface of the vitreous was covered with a pigment layer, similar to the so-called *Pigment-nachstar*.

W. ZENTMAYER.

OPERATIVE TREATMENT OF FIVE CASES OF IRIDODIALYSIS. S. GÖRDÜREN, Brit. J. Ophth. 32: 429 (July) 1948.

Gördüren employs a slight modification of Golowin's operation for the correction of iridodialysis. A keratome incision is made just at the level of the root of the iris and parallel to its anterior surface. The

records of 46 patients with retrobulbar neuritis were taken from the hospital files. Eleven patients were not traced; 4 were dead, and 1 refused examination. The remaining 30 patients were examined from ten to forty-seven years later. Twelve patients were found to have abnormal neurologic signs apart from those referable to the eyes, but only 1 was bedridden with disseminated sclerosis. The eventual prognosis of visual recovery was good. Of the 24 patients with unilateral involvement, 1 was blind; and of the 6 with bilateral disease, 2 were blind in both eyes and 2 were blind in one eye. The importance of examination of cerebrospinal fluid for evidence of syphilis in cases of retrobulbar neuritis is stressed.

W. ZENTMAYER.

RETINAL CHANGES WITH ACUTE REDUCTION OF VISION AS INITIAL SYMPTOMS OF INFECTIOUS MONONUCLEOSIS. G. KARPE and P. WIEING, *Acta ophth.* 26: 19, 1948.

A case of infectious mononucleosis is reported in which an edematous swelling, about 7 D. in elevation, developed in the macular region of the retina of one of the patient's eyes. On recovery of the patient, the swelling subsided, leaving only scattered granules of retinal pigment as an aftermath, with no evidence of underlying choroiditis. This case is regarded as further evidence that infectious mononucleosis possesses a certain neurotropism, in addition to an affinity for the lymphatic organs.

O. P. PERKINS.

PERIPHLEBITIS RETINAE AND ITS RELATION TO THE PRIMARY TUBERCULOUS INFECTION. M. HAARR, *Acta ophth.* 26: 41, 1948.

A survey of the clinical picture of periphlebitis retinae is given. Four cases are reported in which the disease seems to have developed in connection with a primary tuberculous infection elsewhere. It is therefore emphasized that periphlebitis retinae is not an isolated ophthalmic disease but, rather, a localized manifestation of a systemic process. The disease is closely related to erythema nodosum. Other localizations of a perivascular process may occur, such as in the central nervous system, joints, pleura and kidneys.

O. P. PERKINS.

RETINITIS PIGMENTOSA WITH SPECIAL REFERENCE TO OTOLOGIC, NEUROLOGIC AND ENDOCRINE COMPLICATIONS. E. KJERRUMGAARD, *Acta ophth.* 26: 55, 1948.

The author presents a statistical survey of 150 cases of retinitis pigmentosa in several institutions for the blind. Various ocular, otologic, neurologic and endocrine complications, or concomitant findings, are discussed. The author stresses that, though developmental anomalies may be of very different natures and be localized in widely different parts of the body, they may still be the result of one lesion affecting a gene, or group of genes, at a given time in embryonic development.

O. P. PERKINS.

## Book Reviews

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### **Sulla teoria delle aberrazione monochromatiche nell'occhio umano.**

By G. Carlevaro Parma, M.D. Pp. 160, with 153 illustrations.  
Torino, Italy: Resenberg and Sellier, 1943.

This book gives a thorough exposition of the work of von Helmholtz, Tscherning and Gullstrand on the subject of monochromatic aberrations of the eye. Of the three parts, the first is devoted to the presentation of the elements of mathematics necessary to a consideration of the algebraic, geometric and trigonometric aspects, presented in the other two parts. The second part is also introductory in content, since it deals with theories and laws and their application to image formation in general.

Part three contains the author's exposition of the subject, together with his original contributions to it. Keratoscopic findings with the Gullstrand mire permit the classification of corneal asymmetries into three groups, according to the distortion of the corneal reflex in the various meridians and the decentration of the pupil. By a method of subjective stigmatoscopy, the authors and two other subjects made their observations, which are reproduced to show in various cross sections the caustic curve as it is projected on the retina by changing the focus of the eye with lenses placed before it. Thus the composition and distribution of light rays emitted by a luminous point are analyzed as they are refracted in the eye.

The author further discusses, in relation to spherical aberration, decentration of the pupil and of the corneal optic zone, and the path of rays in the astigmatic eye. The application of objective stigmatoscopy and ophthalmoscopy to the problem of monochromatic aberrations of the eye is briefly presented.

The book is carefully planned and presented and yet is easier to follow than is usual with so complete a presentation of this difficult subject.

JOSEPH J. LO-PRESTI.

### **Transactions of the Pacific Coast Oto-Ophthalmological Society, San Francisco, 1948.**

This is the report of the thirty-second annual meeting of the Pacific Coast Oto-Ophthalmological Society, which is patterned after the Academy of Ophthalmology and Otolaryngology. The meetings were held June 7, 8, 9 and 10, 1948, in Seattle. Instructional courses and scientific papers on both ophthalmology and otolaryngology were delivered. A list of papers presented on ophthalmology and their authors follows: "The Roentgen Ray Treatment of Uveitis," Moacyr E. Alvarado, M.D.; "Thyrotropic Exophthalmos: Report of Three Cases Treated Medically," Clarence A. Veasey Jr., M.D.; "Lighting and Visual Efficiency," James R. Powell, M.D.; "Divergence Insufficiency as a Practical Problem," L. Weston Oaks, M.D.; "Accommodative Defect Following Atmospheric Concussion," Homer E. Smith, M.D.; "The Corneal Lens; a New Type of Plastic Contact Lens: A Preliminary Report," Maurice W. Nugent,



knife is slowly withdrawn, and the root of the iris is allowed to come between the lips of the incision with the outflow of aqueous; then, with two spatulas, slight adjustments are made to keep the root of the iris evenly in the lips of the wound. Atropine is instilled, and both eyes are bandaged. In 3 of the cases the iridodialysis was corrected. A deep groove was left in the margin of the pupil.

W. ZENTMAYER.

### Visual Tracts and Fields

WIDENING OF THE ANGIOSCOTOMA IN THE ALARM REACTION. M. R. CHOLST, *Am. J. Ophth.* 31: 821 (July) 1948.

Cholst gives the following summary:

1. In this study the effect of alarm on the angioscotoma and on the possible physiologic mechanism involved is presented.

2. A widening of the angioscotoma was demonstrated in the 3 cases studied; the scotoma gradually returned to normal shortly after the cause was removed.

3. This effect of fright might be a source of error in the mapping of the blindspot when routine central scotometry is performed on subjects in an apprehensive state.

W. S. REESE.

BITEMPORAL VISUAL FIELD DEFECT IN AQUEDUCT STENOSIS. M. BARD-  
RAM, *Acta ophth.* 26: 25, 1948.

The author reports 2 cases of stenosis of the aqueduct in which papilledema and bitemporal field defects were evident. Ventriculographic studies demonstrated a distended third ventricle pressing down into an expanded sella. Hence it is important to consider the possibility of a lesion in the posterior fossa when one is confronted with this combination of signs.

O. P. PERKINS.

# INDEX TO VOLUME 41

The asterisk (\*) preceding the page number indicates an original article in the Archives. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

**Abnormalities and Deformities:** See also under names of organs and regions, as Choroid, absence; Eyelids; Iris, absence; etc.

inheritance of arachnodactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in E. family, \*276

**Abscess:** See under names of organs and regions

**Accommodation and Refraction:** See also Astigmatism; Glasses; Myopia; etc.

clinical aniseikonia, 506

comparison of aniseikonic test instruments and prolonged induction of artificial aniseikonia, 640

reserve accommodation, \*701

sodium-vapor lamp and its use for refraction, 104

studies on effect of certain stimulants on accommodation of eye and of threshold value for effect of vitamin B<sub>1</sub> on accommodation, 355

study of refraction according to technic used by some North American ophthalmologists, 649

voluntary dissociation of accommodation and convergence faculty; 2 observations, \*599

**Acid, Nicotinic:** See Nicotinic Acid

**Adaptation;** widening of angioscotoma in alarm reaction, 764

**Adaptometer:** See Accommodation and Refraction; Vision

**Adenoma of pituitary gland,** \*230

**Adolescence;** corneal grafts in child and adolescent, 640

**Adrenals;** changes in ocular fundus associated with pheochromocytoma of adrenal gland; report of 3 cases, 505

neuroblastoma with orbital metastases, 105

**Aeronautics:** See Aviation and Aviators

**After-Image:** See Vision, physiology

**Agnosia:** See Aphasia

**Agraphia:** See Aphasia

**Air;** metabolism of cornea, \*736

**Air Forces:** See Aviation and Aviators

**Air Passages:** See Respiratory Tract

**Alarm Reaction:** See Adaptation

**Alcohol:** See Orbit

Wood: See Methyl Alcohol

**Alcoholism;** character of nystagmus induced by amytal in chronic alcoholics, 490

**Alexia:** See Aphasia

**Allergy:** See Anaphylaxis and Allergy

**Aluminum and Aluminum Compounds;** effect of aluminum and its alloys on eye, 238

**Amaurosis:** See Blindness

**Amblyopia:** See Blindness

**Ambrose, A.:** Simplified perimeter of wall type, \*633

**Amentia:** See Feeble-mindedness

**American Board of Ophthalmology,** 246, 354

candidates for board examinations, 637

**Ametropia:** See Hyperopia; Myopia

**Amytal:** See Anesthesia

**Anaphylaxis and Allergy;** allergic ocular reaction to tuberculin test; bilateral cyclitis and neuroretinitis, \*436

conjunctival eosinophilia and eosinophilia in blood, 482

relation of allergy to acute iritis, 106

significance of intracutaneous test for hypersensitivity to uveal pigment, 364

xanthelasma and autonomic nervous system; new syndrome, 236

**Anesthesia;** character of nystagmus induced by amytal in chronic alcoholics, 490

motor block of extraocular muscles by deep orbital injection, \*5

**Anesthetics:** See Anesthesia

**Aneurysm;** mechanism of production of massive preretinal hemorrhage following rupture of congenital medial-defect intracranial aneurysm, 364

**Angioid Streaks:** See under Retina

**Angioma;** angiomatosis of retina in infant, 244

histopathologic aspects of retrolental fibroplasia, \*553

indications for contact radiotherapy in treatment of tumors of lids, 763

juxtapapillary hemangioendothelioma of retina; report of case, \*178

of retina; treatment with diathermy, 503

**Angioscotoma:** See Scotoma

**Angiospasm:** See under Retina

**Aniridia:** See Iris, absence

**Aniseikonia:** See Accommodation and Refraction

**Anomalies:** See Abnormalities and Deformities; and under names of organs and regions, as Choroid, absence; Iris, absence; etc.

**Anopsia:** See Blindness

**Antistin®;** tolerance of contact lenses, 649

**Antitoxin:** See Staphylococci

**Aphasia;** agnostic alexia without agraphia following trauma; report of case, 490, 514

developmental, also known as congenital word-blindness and sometimes referred to as alexia or dyslexia, 490

**Aphthae:** See Stomatitis

**Aplasia:** See Nerves, optic

**Apparatus:** See also Instruments

low power infra-red microscope, 645

**Aqueduct of Sylvius:** See under Brain

**Aqueous Humor;** clinical experiments with new ways of influencing intraocular tension; use of rutin to enhance tension-reducing effect of miotics by reducing permeability of blood-aqueous barrier, \*429

effects of nitrogen mustard on permeability of blood-aqueous humor barrier to Evans blue, 641

influence of local arterial blood pressure on aqueous humor and intraocular pressure; experimental study of mechanisms maintaining intraocular pressure, 97

parasympathomimetic effect in human eyes with and without chronic simple glaucoma, 639

pharmacology of blood aqueous barrier, 366

studies of physiology of eye using tracer substances; steady-state ratio of sodium between plasma and aqueous humor in guinea pig, 103

studies on outflow pressure of aqueous in human beings, 103

**Arachnodactyly;** inheritance of arachnodactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in E. family, \*276

**Area Martegiani:** See Vitreous Humor

**Ariboflavinosis:** See Riboflavin

**Armed Forces Personnel:** See Aviation and Aviators; Military Medicine; etc.

**Arsphenamines;** corneal changes during treatment with, 641

**Arteries:** See also Aneurysm; Arteriosclerosis; Blood pressure; Blood vessels; Thrombosis; Vasomotor System; etc.

carotid; treatment of thrombosis of cavernous sinus with intra-arterial injections of penicillin, 365

**Hypertension:** See Blood pressure, high

**Retinal:** See Retina, blood supply

variations in system of trunks of posterior ciliary arteries, 95

M.D.; "Cyclodiathermy—Indications, Technic and Results," Andrew de Roethth, M.D.; "Some Tumors of the Iris," Charles W. Browning, M.D., and Kenneth C. Swan, M.D.; "Hemorrhage Into the Anterior Chamber in Nonperforating Injuries," Robert C. Laughlin, M.D.

FRANCIS HEED ADLER.

**Elementos de cirurgia do cristalino (Tratamento cirurgico da cataracta).** By A. Lopez d'Andrade, Director of the Institute of Ophthalmology of Dr. Gamma Pinto, Professor of Ophthalmology in the Faculty of Medicine of Lisbon, Portugal. Bertrand Brothers, 1947.

This is a practical treatise on the surgical treatment of cataract as carried out in the Institute of Ophthalmology of Dr. Gamma Pinto in Lisbon. It concerns the author's technic primarily, rather than a review of the literature. There are a brief chapter on the embryology and anatomy of the lens and good chapters on the indications for operation for the usual type of cataract and for various atypical forms. The operations are well illustrated with photographs and drawings. There is a good section on postoperative complications and their treatment.

FRANCIS H. ADLER.

**Malattie cutanee e veneree ed alterazione oculari.** By G. Sala and P. Noto, with foreword by Prof. A. Crosti and Prof. B. Alajmo; Edited by S. F. Flaccovio. Price, 1,500 lire. Pp. 410. Palermo, Italy, 1948.

This volume, by an ophthalmologist and a dermatologist, is an important Italian publication, showing the close relation of these two branches of medicine. The authors did not limit their observations to the diseases of the skin surrounding the eye, but made a complete clinical and pathologic study of generalized diseases of the skin affecting the interior of the eye. The volume, of 410 pages, is divided into sixteen chapters, including "Epithelial Dystrophies," "Allergic Dermatoses," "Dermatoses Due to Parasites," "Infection and Avitaminoses," "Precancerous Lesions," "Hemorrhagic Syndrome" and "Venereal Diseases."

A large bibliography completes this interesting and well written book, for which the authors deserve a great deal of credit.

VITO LA ROCCA.

## BOOK REVIEWS—Continued

- Handbook of Ophthalmology; E. L. Goar, 657
- Hofstetter, H. W.: Optometry: Professional Economical and Legal Aspects, 250
- Lopez d'Andrade, A.: Elementos de cirurgia do cristalino (Tratamento cirurgico da cataracta), 766
- Lunenburg, R. K.: Mathematical Analysis of Binocular Vision, 251
- Malattie cutanee e veneree ed alterazione oculari; G. Sala and P. Noto, 766
- Mathematical Analysis of Binocular Vision; R. K. Lunenburg, 251
- Modern Trends in Ophthalmology; A. Sorsby, 654
- Mooney, B.: More Than Armies: Story of Edward H. Cary, M.D., 391
- More Than Armies: Story of Edward H. Cary, M.D.; B. Mooney, 391
- Neurology of Ocular Muscles; D. G. Cogan, 390
- Noto, P.: Malattie cutanee e veneree ed alterazione oculari, 766
- Oculus: Tabulae Biologicae; edited by K. Steindorff and others, 109
- Ophthalmology in War Years; edited by M. Wiener, 110
- Optometry: Professional, Economical and Legal Aspects; H. W. Hofstetter, 250
- Principles and Practice of Ophthalmic Surgery; E. B. Spaeth, 249
- Report of Committee on Trachoma of Second Pan-American Congress of Ophthalmology, 653
- Routier, D.: Fond d'oeil des hypertendus et des cyanoses, 654
- Sala, G.: Malattie cutanee e veneree ed alterazione oculari, 766
- Some Aspects of Oculo-Refractive Technique; M. Cholerton, 658
- Sorsby, A.: Modern Trends in Ophthalmology, 654
- Spaeth, E. B.: Principles and Practice of Ophthalmic Surgery, 249
- Sulla teoria delle aberrazione monochromatiche nell'occhio umano; G. Carlevaro Parma, 765
- Transactions of Pacific Coast Oto-Ophthalmological Society, San Francisco, 1948, 765
- Traquair, H. M.: Clinical Ophthalmology, 392
- von Tschermak-Seysenegg, A.: Einführung in die physiologische Optik, 525
- Wiener, N.: Cybernetics, or Control and Communication in Animal and Machine, 655
- Wolff, E.: Anatomy of Eye and Orbit, 657
- Year Book of Eye, Ear, Nose and Throat; L. Bothman and S. J. Crowe, 658
- Bourneville's Disease: See Sclerosis, tuberous
- Bowen's Disease: See Cancer, precancer
- Bowman Membrane: See under Cornea
- Brain: See also Meninges; Nervous System; Thalamus; etc.
- bitemporal visual field defect in aqueduct stenosis, 764
- blood supply; surgical problem of intracranial aneurysm and allied vascular lesions, 383
- changes in visual fields confirmed by pathologic diagnosis, 387
- Diseases: See also Encephalitis; etc.
- diseases; intracranial origin of glaucomatous atrophy of optic nerve, 486
- edema; ocular syndrome of cataract and papilledema in manifest form of parathyroid deficiency, 498
- Sclerosis: See Sclerosis
- Brakey, A. E.: Experimental studies of inclusion blennorrhoea; isolation of virus, \*151
- Bruce, G. M.: Changes in ocular fundus associated with pheochromocytoma of adrenal gland; report of 3 cases, 505
- Buerger's Disease: See Thromboangitis obliterans
- Bullet Wounds: See Wounds
- Buschke, W. H.: Morphologic changes in cells of corneal epithellum in wound healing, \*306
- Production of cataract in rats by beta-tetralol and other derivatives of naphthalene, \*572
- Calibration of tonometers, problems in, 520, 645
- Canal of Schlemm: See Eyes
- Cancer: See also Epithelioma; and under names of organs and regions, as Eyelids; Orbit; etc.
- precancer; intraepithelial epithelioma of cornea and conjunctiva (Bowen's disease), 651
- Capillaries: See also Blood vessels; Vasomotor System
- fragility and cutaneous lymphatic flow in relation to systemic and retinal vascular manifestations; rutin therapy, 649
- fragility and permeability in relation to retinal hemorrhages, 242
- Cardiovascular System: See Arteries; Vasomotor System; etc.
- Carbon Dioxide; researches on respiration of cornea in albino rats, 234
- Solid: See Cornea
- Carcinoma: See Cancer
- Carrier: See Trachoma
- Caruncle: See Lacrimal Organs
- Cassady, J. V.: Congenital cyst of vitreous; report of case, \*734
- Cataract; acute reversible, in chicken due to various nitrocompounds, 483
- blood protein in certain types of changes in lens, 516
- connection, between position of zonular opacities in lens and time of their formation estimated from simultaneously occurring enamel hypoplasia, 646
- effects of diabetes on cataract and on vision, \*462
- extraction in presence of fluid vitreous, 499
- extraction, total, by massage, 488
- in dystrophia myotonica, \*450
- intracapsular extraction, 645
- intracapsular extraction and detachment of retina, 362
- low power infra-red microscope, 645
- motor block of extraocular muscles by deep orbital injection, \*5
- ocular syndrome of cataract and papilledema in manifest form of parathyroid deficiency, 498
- production in rats by beta-tetralol and other derivatives of naphthalene, \*572
- sight disturbances caused by proliferation of pigment epithellum, 763
- Catgut: See Sutures
- Cauterization: See under names of various organs and diseases, as Iris; Retina; etc.
- Cavernous Sinus, Thrombosis: See Thrombosis
- Cells: See also Tissue
- Inclusion: See Trachoma
- granular cell myoblastoma of orbit; report of 2 cases, 498
- morphologic changes in cells of corneal epithellum in wound healing, \*306
- regeneration of corneal stromal cells; technic for destruction of corneal corpuscles by application of solidified (frozen) carbon dioxide, 756
- ricketsal bodies in epidemic nummular conjunctivitis (epidemic keratoconjunctivitis), 356
- tissue research and cell culture of cornea, 757
- Cephalosporosis: See Mycosis
- Cerebrospinal Fluid; operative technic of vitreous replacement, 107
- Cerebrum: See Brain
- Chemotherapy: See under names of diseases and chemotherapeutic agents, as Conjunctivitis; Cornea, ulcers; Eyes, diseases; Penicillin; Trachoma; etc.
- Chiasm, Optic: See Optic Chiasm

## INDEX TO VOLUME 41

- Arteriosclerosis; capillary fragility and cutaneous lymphatic flow in relation to systemic and retinal vascular manifestations; rutin therapy, 649  
 retinal arteries or arterioles, 481  
 Arthritis: See also Rheumatism  
 rheumatoid; scleromalacia perforans; report of case, \*183  
 Asthenopia; reserve accommodation, \*701  
 Astigmatism; size of line in Maddox-rod test, 645  
 study of refraction according to technique used by some North American ophthalmologists, 649  
 Atherosclerosis: See Arteriosclerosis  
 Atkinson, W. S.: Delayed mustard gas (2-chloroethyl sulfide) keratitis; report of 2 cases, 497  
 Atopy: See Anaphylaxis and Allergy  
 Atrophy: See under names of organs and regions, as Nerves, optic; etc.  
 Atropine methylnitrate; mydriatics; clinical observation, \*50  
 use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583  
 Aub, J. C.: Early photograph of von Helmholtz with explanatory letter, \*570  
 Auditory Organ: See Ear  
 Autographs; studies of eye with radiosodium autographs, \*611  
 Autohemotherapy: See Hordeolosis  
 Autokeratoplasty: See Cornea, ulcer  
 Aviation and Aviators; aviation ophthalmology, 358, 484  
 Avitaminosis: See under names of deficiency diseases  
 Bacteria: See Staphylococci; Viruses; etc.  
 Calmette-Guérin: See Tuberculosis  
 Granulosis: See Trachoma  
 Leprosy: See Leprosy  
 Bailey, P.: Practice of neurology in United States, 377  
 Balanitis: See Penis  
 Barkan, O.: Goniotomy for congenital glaucoma; urgent need for early diagnosis and operation, 373  
 Technic of goniotomy for congenital glaucoma, \*65  
 Barnes, C. K.: Voluntary dissociation of accommodation and convergence faculty; 2 observations, \*599  
 Bedell, A. J.: Diagnosis of retinoblastoma, 513  
 Bell's Palsy: See Paralysis, facial  
 Berens, C.: Modified 3 character test for binocular vision especially applicable to examination of amblyopic children, \*460  
 Berke, R. N.: Congenital ptosis; classification of 200 cases, \*188  
 Metals-Parinaud type of operation for ptosis; report on 35 cases, \*324  
 Besnier-Boeck-Schaumann Disease: See Sarcoidosis  
 Beta Radiation: See Radium  
 Beta-Tetralol: See Naphthalene  
 Billet, E.: Progressive muscular dystrophy involving extraocular muscles; report of case, \*334  
 Biomicroscopy of posterior segment; further simplifications, 489  
 Birth, Premature: See Premature Infants  
 Blepharitis: See Gonorrhea  
 Blepharoplasty: See under Eyelids  
 Blepharoptosis: See Eyelids, ptosis  
 Blindness: See also Ophthalmia neonatorum; Vision; etc.  
 apparent, of new born; gray pseudoatrophy of optic nerve, 243  
 Color: See Color Perception  
 malignant retrobulbar neuritis, \*60  
 modified 3 character test for binocular vision especially applicable to examination of amblyopic children, \*460  
 peripheral and central disturbances of visual fields; aspect of di-ophthalmology, 244  
 Word-Blindness: See Aphasia  
 Blood: See also Erythrocytes  
 Circulation: See Arteries; Capillaries; Vasomotor System; Veins; etc.  
 conjunctival eosinophilia and eosinophilia in blood, 482  
 groups and effects of roentgen irradiation in retrolental fibroplasia, \*659  
 pressure; further gonioscopic studies on canal of Schlemm, \*393  
 pressure, high; capillary fragility and cutaneous lymphatic flow in relation to systemic and retinal vascular manifestations; rutin therapy, 649  
 pressure, high; experimental hypertensive retinopathy, 234  
 pressure, high; falling dogma; ocular hypertension in glaucoma, 759  
 pressure, high; retinal arteries or arterioles, complications in patients with hypertension, 108  
 pressure; influence of local arterial blood pressure on aqueous humor and intraocular pressure; experimental study of mechanisms maintaining intraocular pressure; use of phenylephrine hydrochloride (neo-synephrine hydrochloride®) in ophthalmology, \*172  
 proteins in certain types of changes in studies of physiology of eye using tracer substances; steady-state ratio of sodium between plasma and aqueous humor in guinea pig, 103  
 Vessels: See also Arteries; Capillaries; Vasomotor System; Veins; etc.  
 vessels; tumors of vascular origin, \*204  
 vessels; vascularization of cornea; its experimental induction by small lesions and new theory of its pathogenesis, \*406  
 volume; effects of nitrogen mustard on permeability of blood-aqueous humor barrier to Evans blue, 641  
 Blood-Aqueous Barrier: See Aqueous Humor  
 Body, Mind and Body: See Mind  
 Boeck's Disease: See Sarcoidosis  
 Bones: See under names of bones  
 Diseases: See Osteitis deformans; Osteomyelitis  
 Book Reviews:  
 Anatomy of Eye and Orbit; E. Wolff, 657  
 Bothman, L., and Crowe, S. J.: Year Book of Eye, Ear, Nose and Throat, 658  
 Bulletins et memoires de la Societe française d'ophtalmologie: Sixty Years, 1947, 391  
 Carlevaro Parma, G.: Sulla teoria delle aberrazioni monocromatiche nell'occhio umano, 765  
 Cholerton, M.: Some Aspects of Oculoclinical Ophthalmology; H. M. Traquair, 392  
 Cogan, D. G.: Neurology of Ocular Muscles, 390  
 Crowe, S. J., and Bothman, L.: Year Book of Eye, Ear, Nose and Throat, 658  
 Cybernetics, or Control and Communication in Animal and Machine; N. Wiener, 655  
 Diseases of Fundus Oculi with Atlas; A. Fuchs, 656  
 Documenta Ophthalmologica: Volume II; edited by F. P. Fischer, 249  
 Einführung in die physiologische Optik; A. von Tschermak-Seysenegg, 525  
 Elementos de cirurgia do cristalino (Tratamento cirurgico da cataracta); A. Lopez d'Andrade, 766  
 Fischer, F. P.: Documenta Ophthalmologica: Volume II, 249  
 Fond d'oeil des hypertendus et des cyanoses; D. Routier, 654  
 François, J.: Gonioscopy, 656  
 Fuchs, A.: Diseases of Fundus Oculi with Atlas, 656  
 Goar, E. L.: Handbook of Ophthalmology, 657  
 Gonioscopy; J. François, 656

- Deformities: See also Abnormalities and Deformities; and under names of organs and regions
- Dementia Precox; ocular findings in 323 patients with schizophrenia; preliminary report, \*697
- Denig Operation: See Trachoma
- Dermatitis; use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583
- Dermatoses: See Dermatitis; Skin, diseases; etc.
- Descemet Membrane: See Cornea
- Desmarres Operation: See Pterygium
- de Schweinitz lecture, annual, 637
- Desoxyephedrine; studies on effect of certain stimulants on accommodation of eye and of threshold value for effect of vitamin B<sub>1</sub> on accommodation, 355
- DFF: See Glaucoma
- Diabetes Mellitus; acute retinopathy without hyperplasia in diabetic pregnancy, 492
- capillary fragility and cutaneous lymphatic flow in relation to systemic and retinal vascular manifestations; rutin therapy, 649
- effects of diabetes on cataract and on vision, \*462
- ocular expressions of, 235
- Diathermocoagulation: See Cataract; Glaucoma; Retina, detachment
- Diathermy: See under names of diseases, organs and regions as Angioma; Glaucoma; Retina; etc.
- Dibutoline sulfate; mydriatics; clinical observation, \*52
- Dichloroethyl Sulfide: See Gas, poisoning
- Di-Isopropyl Fluorophosphate: See Glaucoma
- Dillon, B.: Studies of eye with radiosodium autographs, \*611
- Diplegia: See Paralysis
- Diplopia; traumatic pulsating exophthalmos; report of case, 491
- Directory of ophthalmologic societies, 111
- Disk, Choked: See Neuritis, optic
- Optic: See Nerves, optic
- Dixon, J. M.: Tuberculous sclerosis in 3 siblings, \*473
- Drugs; ocular effect of several irritant drugs applied directly to conjunctiva, 648
- Drusen: See Nerves, optic
- Dry Ice: See under Cornea
- Duane, T. D.: Metabolism of cornea, \*736
- Ductless Glands: See Endocrine Glands
- Dunnington, J. H.: Granular cell myoblastoma of orbit; report of 2 cases, 498
- Dyslexia: See Aphasia; Reading
- Dystrophy, muscular; cataract in dystrophia myotonica, \*450
- muscular, progressive, involving extraocular muscles; report of case, \*334
- Ear; interstitial keratitis and vestibuloauditory symptoms following vaccination, \*24
- retinitis pigmentosa with reference to otologic, neurologic and endocrine complications, 762
- Echinococcosis; hydatid of orbit, 647
- Ectoderm; development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 481
- Ectopia Lentis: See Lens, Crystalline
- Edema: See also under Brain
- problem of glaucoma, 99
- Education; American Orthoptic Council, 637
- annual postgraduate ophthalmologic conference, Department of Postgraduate Medicine of University of Michigan, 246
- postgraduate lectures, University of Glasgow, 750
- Eggers, H.: Reserve accommodation, \*701
- Electrocoagulation: See under specific headings, as Angioma; Glaucoma; Retina; etc.
- Electrodes; contact lens electrode for iontophoresis, \*730
- Electrosurgery: See under specific headings
- Elliot Operation: See under Glaucoma
- Embolism: See Thrombosis
- Enamel; connection between position of zonular opacities in lens and time of their formation estimated from simultaneously occurring enamel hypoplasia, 646
- Encephalitis; interstitial keratitis and vestibuloauditory symptoms following vaccination, \*24
- Endarteritis: See Thromboangiitis obliterans
- Endocrine Glands; retinitis pigmentosa with reference to otologic, neurologic and endocrine complications, 762
- Endovascularitis: See Retina, blood supply
- Entropion: See under Eyelids
- Enucleation: See under Eyes; Orbit; etc.
- Eosinophilia, conjunctival, and eosinophilia in blood, 482
- grave manifestations of gold therapy in cornea and skin, 96
- Epicanthus: See under Eyelids
- Epidermis: See Skin
- Epipharynx: See Nasopharynx
- Episcleritis: See Sclera
- Epithelioma, choroidal metastasis of testicular chorionic epithelioma; report of case, \*587
- intraepithelial, of cornea and conjunctiva (Bowen's disease), 651
- indications for contact radiotherapy in treatment of tumors of lids, 763
- Epithelium: See also Cornea; Lens, Crystalline
- morphologic changes in cells of corneal epithelium in wound healing, \*306
- sight disturbances caused by proliferation of pigment epithelium, 763
- Erythema multiforme; Stevens-Johnson syndrome, 234
- Erythrocytes, stimulation of corneal epithelization with topical application of, 640
- Esophoria: See Phorias; Strabismus
- Eucatropine hydrochloride U.S.P.; mydriatics; clinical observation, \*52
- Eumydrin: See Atropine methylnitrate
- Evans, T. C.: Studies of eye with radiosodium autographs, \*611
- Evans Blue: See Blood, volume
- Evisceration: See under Eyes
- Exophoria: See Strabismus
- Exophthalmos in relation to orbital tumors; report of 8 cases, 102
- traumatic pulsating; report of case, 491
- virus studies in lymphomatoid diseases of ocular adnexa, 642
- with intermittent aggravation; special form of variable exophthalmos, 242
- Eyelashes; treatment of pediculosis ciliaris with anticholinesterase agents; report of case, \*627
- Eyelids: See also Conjunctiva; Conjunctivitis
- discoloration from yellow mercuric oxide, 496
- myxosarcoma of, \*317
- operative procedure for entropion of upper lid, 363
- pigmentation of palpebral conjunctiva resulting from mascara, 356
- Pityrosporum ovale in seborrheic blepharitis and conjunctivitis, 489
- ptosis, congenital; classification of 200 cases, \*188
- ptosis; correction by tucking of levator, 646
- ptosis; Motais-Parinaud type of operation for ptosis; report on 35 cases, \*324
- ptosis; progressive muscular dystrophy involving extraocular muscles; report of case, \*334
- sleep with half-open eyes (physiologic lagophthalmus), 489
- treatment of ulcerative blepharitis with gramicidin, 364
- tumors; indications for contact radiotherapy in treatment, 763
- use of propionates in ophthalmology, \*83
- Eyes: See also Orbit; Vision; and under names of special structures and diseases
- Abnormalities: See under names of special structures of eye, as Iris, absence; etc.
- Accommodation: See Accommodation and Refraction
- action of pilocarpine on normal eyes, 492
- Anesthesia: See Anesthesia
- Anomalies: See under names of special structures of eye and diseases
- Blood Supply: See also Retina, blood supply

- Children: See also Infants  
 comparison of eye conditions among 1,000 reading failures, 500 ophthalmic patients, and 150 unselected children, 642  
 corneal grafts in child and adolescent, 640  
 modified 3 character test for binocular vision especially applicable to examination of amblyopic children, \*460  
 reading difficulty (dyslexia) from ophthalmic point of view, 642
- Chloroethyl Sulfide: See Gas, poisoning
- Chloroethylamines; effects of nitrogen mustard on permeability of blood-aqueous humor barrier to Evans blue, 641
- Choked Disk: See Neuritis, optic
- Cholinesterase; treatment of pediculosis ciliaris with anticholinesterase agents; report of case, \*627
- Chondrosarcoma of orbit, 651
- Chronic Epithelioma: See Epithelioma
- Choroid, absence; discovery and histopathologic study of case of choroideremia, 356  
 choroidal metastasis of testicular chorionic epithelioma; report of case, \*587  
 chronic glaucoma and minimal elective vasodilatation, 361  
 metastatic osteosarcoma in, 494  
 study of pigment cells of choroid in chick embryo, 95  
 traumatic choroiditis; review of literature and report of 10 cases, \*341
- Choroideremia: See Choroid, absence
- Choroiditis: See under Choroid
- Cilia: See Eyelashes
- Ciliary Body: See Iridocyclitis; Uvea  
 Processes: See Uvea  
 Region: See Uvea
- Clinics; Barbara Gregg Ingalls Orthoptic Clinic, 524
- Cogan, D. G.: Treatment of pediculosis ciliaris with anticholinesterase agents; report of case, \*627  
 Vascularization of cornea; its experimental induction by small lesions and new theory of its pathogenesis, \*406
- Cohen, M.: Ocular findings in 323 patients with schizophrenia; preliminary report, \*697
- Coloboma: See Nerves, optic
- Color Perception: See also Vision, physiology  
 qualitative and quantitative perimetry with monochromatic targets and with white targets of same luminous intensity, 240  
 responses to Ishihara test for, \*20
- Congress: See Societies
- Conjunctiva, Catarrh: See Conjunctivitis, vernal  
 conjunctival eosinophilia and eosinophilia in blood, 482  
 experimental studies of inclusion blenor-rhea; isolation of virus, \*151  
 Granular: See Trachoma  
 intraepithelial epithelioma of cornea and conjunctiva (Bowen's disease), 651  
 myxohemangioma simplex of conjunctiva bulbi, 763  
 ocular effect of several irritant drugs applied directly to, 648  
 pigmentation of palpebral conjunctiva resulting from mascara, 356  
 results obtained by total conjunctival hooding of cornea for serpiginous ulcer, 756
- Conjunctivitis: See also Keratoconjunctivitis; Ophthalmia  
 clinical signs of diagnostic importance in, 370  
 eruptive fever with involvement of respiratory tract, conjunctivitis, stomatitis and balanitis, 97  
 Pannus: See Trachoma  
 Pityrosporum ovale in seborrheic blepharitis and conjunctivitis, 489  
 rickettsial bodies in epidemic nummular conjunctivitis (epidemic keratoconjunctivitis), 356  
 role of nasopharyngeal infections in and resistance to treatment of certain types of, 481
- Conjunctivitis—Continued  
 use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583  
 use of propionates in ophthalmology, \*83  
 vernal; beta radiation therapy, \*1  
 with membrane formation, 96
- Contact Lens: See Glasses
- Contusions: See Cataract; Eyes injuries; etc.
- Convergence: See Phorias; Strabismus
- Cordes, F. C.: Ophthalmology's postwar responsibilities and opportunities, 369
- Cornea; acute ocular manifestations of ariboflavinosis, 643  
 blood staining of, 96  
 blood supply; vascularization of cornea; its experimental induction by small lesions and new theory of its pathogenesis, \*406  
 changes during treatment with arsphenamine, 641.  
 diseases; beta radiation therapy, \*1  
 diseases, results of plessiotherapy for, 357
- Fistula: See Fistula  
 glaucoma and leukoma adherens, 487  
 grafts in child and adolescent, 640  
 grafts in 2 patients with Groenow's disease, 641  
 grave manifestations of gold therapy in cornea and skin, 96  
 in defense of nonpenetrating graft, 483
- Inflammation: See Keratitis; Keratoconjunctivitis
- Intraepithelial epithelioma of cornea and conjunctiva (Bowen's disease), 651
- lesions in Hodgkin's disease, 235
- metabolism of, \*736
- morphologic changes in cells of corneal epithelium in wound healing, \*306
- necrosis; scleromalacia perforans; report of case, \*183
- Pannus: See Trachoma
- pharmacology and toxicology of; contemporary concepts, \*253
- regeneration of corneal stromal cells; technique for destruction of corneal corpuscles by application of solidified (frozen) carbon dioxide, 756
- respiration, cyanide inhibition of, 640
- respiration; some researches in albino rats, 234
- stimulation of corneal epithelization with topical application of erythrocytes, 640
- Surgery: See Cataract; Glaucoma
- Syphilis: See Keratitis, interstitial
- tissue research and cell culture of, 757
- transplantation; recent advances in ophthalmic surgery, 241
- ulcers; antitoxin treatment of staphylococcal corneal ulceration, 96  
 ulcers, perforated; treatment by autoplasmic scleral transplantation, 233  
 ulcers; results obtained by total conjunctival hooding of cornea for serpiginous ulcer, 756
- Vascularization: See Cornea, blood supply
- Cosmetics; pigmentation of palpebral conjunctiva resulting from mascara, 356
- Cranium; fundus in fresh gunshot wounds of skull, 100  
 treatment of septic diseases of eye and cranium with infusions of sulfonamide compounds through lower nasal conchas, 495
- Crystalline Lens: See Lens, Crystalline
- Cyanide inhibition of corneal respiration, 640
- Cyclitis: See Iridocyclitis
- Cyclodialysis: See Glaucoma
- Cyclodialthermy: See Glaucoma
- Cysticercosis: See under Echinococcosis
- Cysts: See under names of organs and regions, as Iris; Vitreous Humor; etc.  
 Hydatid: See Echinococcosis
- Cytology: See Cells
- Dacryocystitis: See Lacrimal Organs
- Dacryocystorhinostomy: See Lacrimal Organs
- Dark Adaptation: See Accommodation and Refraction

- Gifford, H., Jr.: Motor block of extraocular muscles by deep orbital injection, \*5
- Glasses: See also Accommodation and Refraction  
 contact lens electrode for iontophoresis, \*730  
 contact, recent experiences with use of, 358  
 tolerance of contact lenses, 649
- Glaucoma: See also Tension  
 and leukoma adherens, 487  
 and provocative tests, 758  
 and thalamus, 360  
 appreciation and mechanism of destructive effects produced by ocular hypertension, 237  
 chronic, and minimal elective vasodilatation, 361  
 chronic, clinical use of di-isopropyl fluorophosphate (DFP) in, 644  
 congenital, goniotomy for; urgent need for early diagnosis and operation, 373  
 congenital, technic of goniotomy for, \*65  
 diathermy cauterization of ciliary body for, \*417  
 early, diagnosis of, 485  
 effectiveness of modified cyclodialysis, 237  
 falling dogma; ocular hypertension in glaucoma, 759  
 fistula of cornea, 482  
 general and local neurovegetative system in patients with primary glaucoma, 99  
 goniodialysis, 486  
 incomplete, 237  
 intracranial origin of glaucomatous atrophy of optic nerve, 486  
 intraocular pressure of normal and glaucomatous eyes as affected by accessory light stimuli, 758  
 iridencleisis in treatment of glaucoma secondary to iridocyclitis, 361  
 mild, 758  
 parasympathomimetic effect of aqueous humor in human eyes with and without chronic simple glaucoma, 639  
 primary, significance of base pressure in, 515  
 problem of, 99  
 reoperation for, 644  
 role of inheritance in, \*125  
 secondary to fibrocystic disease of bone, 644  
 statistical study of, 644  
 studies on outflow pressure of aqueous in human beings, 103  
 technic of nonpenetrating cyclodialthermy, 236  
 use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583
- Glioma; intraorbital tumors, \*223  
 retinoblastoma (retinal glioma) cured by radon seeds; report of case, \*32
- Goiter: See also Exophthalmos  
 some vulgar errors in regard to, 359
- Gold and Gold Compounds; grave manifestations of gold therapy in cornea and skin, 96
- Goldsmith, J.: Neurofibromatosis associated with tumors of optic papilla; report of case, \*718
- Gonin's Operation: See Retina, detachment
- Goniodialysis: See Glaucoma
- Gonioscopy: See Eyes, examination
- Goniotomy: See Glaucoma
- Gonorrhea; experimental studies of inclusion blennorrhea; isolation of virus, \*151
- Gordon, B. L.: Effects of diabetes on cataract and on vision, \*462
- Graduate Work: See Education
- Grafts: See under Cornea; Eyelids; etc.
- Gramicidin: See Eyelids
- Grant, W. M.: Treatment of pediculosis ciliaris with anticholinesterase agents; report of case, \*627
- Granuloma, Malignant: See Hodgkin's Disease
- Greear, J. N.: Use of buccal mucosa in restoration of orbital socket, 511
- Grönblad-Strandberg Syndrome: See Pseudoxanthoma elasticum; Retina, blood supply
- Groenow's Disease: See under Cornea
- Gunn Phenomenon: See Jaw-Winking Phenomenon
- Gunshot Wounds: See Wounds
- Harbater, M.: Scleromalacia perforans; report of case, \*183
- Harrington, D. O.: Ocular manifestations of psychosomatic disorders, 381
- Hay Fever: See Anaphylaxis and Allergy
- Head: See also Cranium  
 injuries; agnostic alexia without agraphia following trauma, 490, 514
- Heart, abnormalities; inheritance of arachnodactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in E. family, \*276
- Heath, P.: Mikulicz' disease and Mikulicz' syndrome, 512  
 Use of phenylephrine hydrochloride (neosynephrine hydrochloride®) in ophthalmology, \*172
- Heine-Medin's Disease: See Poliomyelitis
- von Helmholtz; early photograph with explanatory letter, \*570
- Hemangioendothelioma, juxtapapillary, of retina; report of case, \*178
- Hematology: See Blood
- Hemicyclodialysis: See Glaucoma
- Hemopoietic System: See also Blood  
 tumors of, \*206
- Hemorrhage: See under Eyes; Meninges; Retina; etc.
- Heredity; inheritance of retinoblastoma; 2 families supplying evidence, 376  
 role of inheritance in glaucoma, \*125
- Heterophoria: See Phorias; Strabismus
- Heterotropia: See Strabismus
- von Hippel's Disease: See Angioma; Retina
- Histamine; use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583
- Hodgkin's Disease, corneal lesions in, 235
- Homatropine hydrobromide; mydriatics; clinical observation, \*49
- Hordeolosis, autohemotherapy in, 489
- Hormones: See Endocrine Glands; etc.
- Hughes, W. L.: Integrated artificial eye and "vitallium" implants; further observations, 502
- Hunt, W. T., Jr.: Ophthalmopathy of hypothyroid origin, 508
- Hyaloid Canal: See under Vitreous Humor
- Hydatid Cyst: See Echinococcosis
- Hydrogen Ion Concentration: See under Tissue
- Hyperergy: See Anaphylaxis and Allergy
- Hypermetropia: See Hyperopia
- Hyperopia; subjective procedure for measuring ametropia without test chart or glasses by use of variable bayonet, 648
- Hypertension: See Blood pressure, high  
 Ocular: See Tension
- Hypertonia: See Tension
- Hypheemia: See Eyes, hemorrhage
- Hypophysis: See Pituitary Body
- Hypopyon: See Cornea, ulcers
- Hypotony: See Tension
- Idiocy: See Feeble-mindedness
- Illumination: See Lighting
- Imbecility: See Feeble-mindedness
- Immunity: See Anaphylaxis and Allergy; etc.
- Inclusion Bodies: See Trachoma
- Industrial Diseases: See also Mines and Miners  
 industrial ophthalmology as of 1946, 369
- Infantile Paralysis: See Poliomyelitis
- Infants: See also Children  
 angiomas of retina in, 244  
 dacryocystitis of infancy, 362  
 Newborn: See Newborn Infants  
 Premature: See Premature Infants
- Inflammation, Corneal: See Keratitis
- Ocular: See Ophthalmia; and under special structures of eyes
- Infra-Red Rays; low power infra-red microscope, 645
- Ingalls, Barbara Gregg, Orthoptic Clinic, 524
- Injuries: See under names of organs and regions, as Eyes; Head; Lens, Crystalline; etc.
- Instruments: See also Apparatus  
 beta radiation therapy, \*1  
 comparison of aniseikonic test instruments and prolonged induction of artificial aniseikonia, 640



## Eyes—Continued

- blood supply; condition of ocular vessels in endarteritis obliterans (Winlwarter-Buerger), 485
- comparison of eye conditions among 1,000 reading failures, 500 ophthalmic patients, and 150 unselected children, 642
- Cysts: See under names of special structures of eye
- differential diagnosis of Boeck's sarcoidosis; report of 10 cases with ocular involvement, \*667
- Diseases: See also Iridocyclitis; Glaucoma; Ophthalmia; Trachoma; etc.
- diseases; beta radiation therapy, \*1
- diseases; further simplifications of bio-microscopy of posterior segment, 489
- diseases; intravitreal use of streptomycin, \*629
- diseases; ophthalmopathy of thyroipituitary origin, 508
- diseases; relation of cutaneous diseases and ocular lesions, 98
- diseases; treatment of septic diseases of eye and cranium with infusions of sulfonamide compounds through lower nasal conchas, 495
- diseases; use of phenylephrine hydrochloride (neo-synephrine hydrochloride®) in ophthalmology, \*172
- diseases; use of propionates in ophthalmology, \*83
- effect of aluminum and its alloys on eye, 238
- Enucleation: See Eyes, surgery
- Examination: See also Accommodation and Refraction; Foreign Bodies; Vision, tests; etc.
- examination; appearance of normal fundus as studied by stereo-ophthalmoscopy, 239
- examination; gonioscopy, 364
- examination; investigation in variable monochromatic light of outer vessels of eye, 101
- Foreign Bodies in: See Foreign Bodies, further gonioscopic studies on canal of Schlemm, \*393
- Gonorrhea: See Gonorrhea
- Humors: See Aqueous Humor; Tension; Vitreous Humor
- Injuries: See also under Cataract; Foreign Bodies
- injuries; attempt to treat perforated eye with subconjunctival penicillin, 107
- injuries; indirect gunshot injury of eye simulating Elliot's trephining operation, 239
- injuries; ocular traumatology, 487
- injuries; statistical study of 418 penetrating wounds of globe treated at Hotel Dieu between 1940 and 1945, 361
- injuries; tissue therapy of traumatic changes of vitreous in period of World War II, 108
- injuries; traumatic choroiditis; review of literature and report of 10 cases, \*341
- injuries; traumatic cysts of iris due to epithelial implantation, 759
- integrated artificial eye and "vitallium" implants; further observations, 502, 760
- malignant melanoma of globe, 494
- manifestations of psychosomatic disorders, 381
- Movements: See also Nystagmus; Paralysis; Strabismus; etc.
- movements; supposed torsion of eye around visual axis in oblique directions of gaze, \*704
- Muscles: See also Orthoptics; Paralysis; Phorias; Strabismus
- muscles; congenital syndrome of retraction of globe (new variety), 491
- muscles; muscle schemas, 245
- muscles; surgical correction of paresis of superior oblique, 490
- new concepts concerning ocular complications following vaccination, 643
- ocular changes in acute disseminated lupus erythematosus, 235
- ocular expression of diabetes, 235
- ocular findings in 323 patients with schizophrenia; preliminary report, \*697

## Eyes—Continued

- ocular symptoms of poliomyelitis, 240
- Paralysis: See Paralysis
- parasites; chronic superficial punctate keratitis caused by onchocerci volvulus, 647
- Physiology: See Vision, physiology
- Pigmentation: See Retinitis pigmentosa; and under special structures of eyes
- Proptosis: See Exophthalmos
- pseudosinusitis of newborn and young infant, 102
- reading difficulty (dyslexia) from ophthalmic point of view, 642
- Refraction: See Accommodation and Refraction
- Stevens-Johnson syndrome, 234
- studies with radiosodium autographs, \*611
- Surgery, 760. See also under Cataract; Cornea; Glaucoma; etc.
- surgery, nylon thread in, 241
- Tension: See Glaucoma; Tension
- Tuberculosis: See Tuberculosis
- tumors, pigmented, 105
- Tyndall phenomenon in anterior chamber, 355
- xeroderma pigmentosum with affection of, 757
- year in Xoquiplan leprosarium, 485
- Face, Paralysis: See Paralysis
- Falls, H. F.: Inheritance of retinoblastoma; 2 families supplying evidence, 376
- Farber, D. N.: Cataract in dystrophia myotonica, \*450
- Feeble-mindedness associated with tumors of optic papilla; report of case, \*718
- Feldman, J. B.: Mydriatics; clinical observation, \*42
- Felix-Well Reaction: See Trachoma
- Fetus: See Pregnancy
- Fever, eruptive, with involvement of respiratory tract, conjunctivitis, stomatitis and balanitis, 97
- Mucocutaneous: See Erythema multiforme
- Filatov Method: See Retinitis pigmentosa
- Fingers and Toes, Abnormalities: See Arachnodactyly
- Fistula, corneal, pathology and therapy of, 357
- of cornea, 482
- Fitzhugh, O. G.: Production of cataract in rats by beta-tetralol and other derivatives of naphthalene, \*572
- Flavones; capillary fragility and capillary permeability in relation to retinal hemorrhages, 242
- clinical experiments with new ways of influencing intraocular tension; use of rutin to enhance tension-reducing effect of miotics by reducing permeability of blood-aqueous barrier, \*429
- Fluorescein; pharmacology of blood aqueous barrier, 366
- Flying: See Aviation and Aviators
- Foramen Hyaloideae: See Vitreous Humor
- Foreign Bodies; effect of aluminum and its alloys on eye, 238
- ocular traumatology, 487
- Fovea Centralis: See Macula Lutea
- Fralick, F. B.: Use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583
- Friedenwald, J. S.: Problems in calibration of tonometers, 520
- Fuchs, A.: Malignant retrobulbar neuritis, \*60
- Fundus Oculi: See under Retina
- Gartner, S.: Progressive muscular dystrophy involving extraocular muscles; report of case, \*334
- Gas, poisoning; delayed mustard gas (2-chloroethyl sulfide) keratitis; report of 2 cases, 497
- Geiter, C. W.: Use of phenylephrine hydrochloride (neo-synephrine hydrochloride®) in ophthalmology, \*172
- Genetics: See Heredity
- Gifford, B. L.: Differential diagnosis of Boeck's sarcoidosis; report of 10 cases with ocular involvement, \*687

- McCulloch, J. C., awarded Reeve Prize, 248  
 Macule, J. P.: Clinical aniseikonia, 506  
 Macula Lutea: See also Vision  
   degenerative diseases of, 368  
   Grönblad-Strandberg syndrome, with disciform degeneration of, 649  
   surgical cure of detachment of retina with perforation of macula; report of case, 243  
   tuberculosis, clinical forms of, 366  
 Maddox Rod: See Astigmatism  
 Malformations: See Abnormalities and Deformities; and under names of organs and regions  
 Marfan's Syndrome: See Arachnodactyly  
 Márquez, M.: Supposed torsion of eye around visual axis in oblique directions of gaze, \*704  
 Martin, J.: Surgical problem of intracranial aneurysm and allied vascular lesions, 383  
 Mascara: See Cosmetics  
 Massage, total extraction of cataract by, 488  
 Maxilla: See Jaws  
 Medals: See Awards  
 Medical Societies: See Societies  
 Medicine: See Ophthalmology; etc.  
   Military: See Military Medicine  
   Psychosomatic: See Mind, body and mind  
 Medin-Heine's Disease: See Poliomyelitis  
 Melbomian Gland: See Eyelids  
 Melanoma, diffuse malignant, of iris; report of cases, 518  
   malignant, \*229  
   malignant, of globe, 494  
   of papilla; report of case, 651  
   origin of malignant melanomata, 106  
   pigmented tumors, 105  
   xeroderma pigmentosum with affection of eye, 757  
 Meninges, hemorrhage; mechanism of production of massive preretinal hemorrhage following rupture of congenital medial-defect intracranial aneurysm, 364  
   neural and meningeal tumors, \*215  
 Meningioma; intraorbital tumors, \*217  
 Mercuric oxide, yellow, discoloration of eyelids from, 496  
 Mesenchyme: See Mesoderm and Mesodermal Tissues  
 Mesoderm and Mesodermal Tissues; mesenchymal tumors, \*198  
 Metabolism of cornea, \*736  
 Metals; integrated artificial eye and "vitalium" implants; further observations, 502, 760  
 Methyl Alcohol; toxic disorders of chiasm, 364  
 Meyer, S. J.: Diathermy cauterization of ciliary body for glaucoma, \*417  
 Microscope; low power infra-red microscope, 645  
 Mikulicz' Disease and syndrome, 512, 757  
 Miles, P. W.: Tuberculous sclerosis in 3 siblings, \*473  
 Military Medicine: See also Aviation and Aviators; Gas, poisoning; etc.  
   tissue therapy of traumatic changes of vitreous in period of World War II, 108  
 Mind, body and mind; ocular manifestations of psychosomatic disorders, 381  
 Mines and Miners; pathogenesis and pathophysiology of coal miner's nystagmus, 241  
 Miosis: See Pupils  
 Miotics: See Pupils  
 Mochle, W.: Myxosarcoma of eyelids, \*317  
 Mononucleosis, infectious, retinal changes with acute reduction of vision as initial symptoms of, 762  
 Morphea: See Scleroderma  
 Motais-Parinaud Operation: See Eyelids, ptosis  
 Mouth, inflammation: See Stomatitis  
   use of buccal mucosa in restoration of orbital socket, 511  
 Mucous Membrane; use of buccal mucosa in restoration of orbital socket, 511  
 Mumps: See Parotitis  
 Muscles, Ciliary: See Eyes, muscles  
   correction of ptosis by tucking of levator, 646  
   motor block of extraocular muscles by deep orbital injection, \*5  
 Muscles—Continued  
   Ocular: See Eyes, muscles; Strabismus  
   progressive muscular dystrophy involving extraocular muscles; report of case, \*334  
   Paralysis: See Paralysis  
   surgical approach to inferior oblique muscle, \*607  
   technic for muscle resection without use of Prince forceps, 760  
   use of masseter, temporalis and frontalis muscles in correction of facial paralysis, 241  
 Mustard Gas: See Gas, poisoning  
 Mycosis; Cephalosporium keratitis, 233  
 Mydriatics: See Pupils  
 Myoblastoma, granular cell, of orbit; report of 2 cases, 498  
 Myocampter: See Strabismus  
 Myopia; effect of visual training on existing myopia, 104  
   subjective procedure for measuring ametropia without test chart or glasses by use of variable bayonet, 648  
 Myotonia, Dystrophica: See Dystrophy, muscular  
 Myxohemangioma simplex of conjunctiva bulbi, 763  
 Myxosarcoma of eyelids, \*317  
 Naphthalene, production of cataract in rats by beta-tetralol and other derivatives of, \*572  
 Narcosis: See Anesthesia  
 Nasolacrimal Duct: See Lacrimal Organs  
 Nasopharynx; role of nasopharyngeal infections in and resistance to treatment of certain types of conjunctivitis, 481  
 Nearsightedness: See Myopia  
 Necrosis: See Cornea  
 Needling: See Cataract  
 Neel, J. V.: Inheritance of arachnodactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in E. family, \*276  
 Neoplasms: See Cancer; Tumors  
 Neo-Synephrine; use of phenylephrine hydrochloride (neo-synephrine hydrochloride®) in ophthalmology, \*172  
 Nerves: See also Nervous System; Neuritis; Paralysis; etc.  
   Blocking: See Anesthesia  
   optic; analysis of fiber-size in human optic nerve, 355  
   optic; development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 481  
   optic; apparent blindness of newborn; gray pseudotrophy of optic nerve, 243  
   optic, atrophy; toxic disorders of chiasm, 364  
   optic; bilateral coloboma of optic disk, 482  
   optic; crater-like holes in optic disk, 640  
   optic; hereditary aplasia in mouse, 233  
   optic, intracranial origin of glaucomatous atrophy of optic nerve, 486  
   optic; melanoma of papilla; report of case, 651  
   optic; neurofibromatosis associated with tumors of optic papilla; report of case, \*718  
   optic; ocular findings in 323 patients with schizophrenia; preliminary report, \*697  
   Paralysis: See under Paralysis  
 Nervous System: See also Brain; Nerves; etc.  
   autonomic, and xanthelasma; new syndrome, 236  
   general and local neurovegetative system in patients with primary glaucoma, 99  
   neural and meningeal tumors, \*215  
   parasympathomimetic effect of aqueous humor in human eyes with and without chronic simple glaucoma, 639  
   retinitis pigmentosa with reference to otologic, neurologic and endocrine complications, 762  
   Tumors: See Neuroblastoma; Neurofibroma; Neuroma; etc.  
 Neuritis, epidemic retrobulbar, in Philippines during Japanese occupation, 104  
 malignant retrobulbar, \*60

- Instruments—Continued**  
 contact lens electrode for iontophoresis, \*730  
 simple, self-registering perimeter, 645  
 simplified perimeter of wall type, \*633  
 subjective procedure for measuring ametropia without test chart or glasses by use of variable bayonet, 648
- Insulin:** See Diabetes Mellitus
- Internal Secretions:** See Endocrine Glands
- Intraocular Tension:** See Glaucoma; Tension
- Ion Transfer;** contact lens electrode for iontophoresis, \*730
- Iontophoresis:** See Ion Transfer
- Iridectomy:** See under Cataract; Glaucoma; Iris
- Iridencleisis:** See Glaucoma
- Iridocyclitis:** See also Ophthalmia, sympathetic  
 allergic ocular reaction to tuberculin test; bilateral cyclitis and neuroretinitis, \*436  
 fistula of cornea, 482  
 iridencleisis in treatment of glaucoma secondary to, 361
- Iridodialysis:** See also Glaucoma; Iris
- Iris:** See also Pupils  
 absence; aniridia with pedigree, 482  
 cysts, traumatic, due to epithelial implantation, 759  
 diffuse malignant melanoma of; report of cases, 518  
 inflammation: See also Iridocyclitis  
 inflammation; relation of allergy to acute iritis, 106  
 operative treatment of 5 cases of iridodialysis, 763  
 sight disturbances caused by proliferation of pigment epithelium, 763
- Iritis:** See Iris, inflammation
- Ishihara Test:** See Color Perception
- Jaw-Winking Phenomenon;** Marcus Gunn phenomenon, 356
- Jaws;** pseudosinusitis of newborn and young infant, 102
- Johnson, W. F.:** Surgical approach to inferior oblique muscle, \*607
- Johnson-Stevens Disease:** See Erythema multiforme
- Joy, H. F.:** Agnostic alexia without agraphia following trauma; report of case, 514
- Kambara, G. K.:** Choroidal metastasis of testicular chorionic epithelioma; report of case, \*587
- Keratotomy:** See under Cornea
- Keratitis:** See also Keratoconjunctivitis  
 Cephalosporium, 233  
 chronic superficial punctate keratitis caused by onchocercal volvulus, 647  
 delayed mustard gas (2-chloroethyl sulfide) keratitis; report of 2 cases, 497
- Groenouw's:** See Cornea
- Interstitial, and penicillin,** 756
- Interstitial, and vestibuloauditory symptoms following vaccination,** \*24
- Interstitial, penicillin in,** 755
- new concepts concerning ocular complications following vaccination,** 643
- ocular manifestations of mumps,** 235
- Trachomatous:** See Trachoma
- use of propionates in ophthalmology,** \*83
- Keratoconjunctivitis;** rickettsial bodies in epidemic nummular conjunctivitis (epidemic keratoconjunctivitis), 356  
 syndrome of Sjögren, 98
- Keratoplasty:** See under Cornea
- Kless, R. D.:** Use of antihistaminic drugs in control of atropine dermatitis and conjunctivitis, \*583
- Kirby, D. B.:** Extraction of cataract in presence of fluid vitreous, 499
- Klein, B. A.:** Histopathologic aspects of retrolental fibroplasia, \*553
- Knapp, A.:** John Elmer Weeks, 752
- Koch, E. L. P.:** Pupillometry; critique, 521
- Koyanagi-Vogt Syndrome:** See under Uvea, inflammation
- Krause, A. C.:** Differential diagnosis of Boeck's sarcoidosis; report of 10 cases with ocular involvement, \*667
- Kronfeld, P. C.:** Further gonioscopic studies on canal of Schlemm, \*393
- Kuhn, H. S.:** Industrial ophthalmology as of 1946, 369
- Lacrimal Canal:** See Lacrimal Organs
- Lacrimal Organs;** advantageous modification of dacryocystorhinostomy, 100  
 dacryocystitis of infancy, 362  
 mixed tumor of lacrimal gland, \*210  
 technic of application of sutures in dacryocystorhinostomy, 362  
 technical contributions to dacryocystorhinostomy, 100  
 treatment of stenosis of lacrimal duct, 487
- Lagophthalmus:** See under Eyelids
- Lamina Sclerae:** See Sclera
- Vitreous:** See Choroid
- Lectures;** annual de Schweinitz lecture, 637
- ophthalmology, Royal College of Surgeons of England,** 638  
 postgraduate, University of Glasgow, 750
- Lens, Contact:** See Glasses
- Lens, Crystalline;** blood groups and effects of roentgen irradiation in retrolental fibroplasia, \*659  
 blood protein in certain types of changes in lens, 516  
 connection between position of zonular opacities in lens and time of their formation estimated from simultaneously occurring enamel hypoplasia, 646  
 histopathologic aspects of retrolental fibroplasia, \*553  
 induction of experimental tumor, 484  
 inheritance of arachnoidactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in E. family, \*276
- Opacity:** See Cataract
- persistence and hyperplasia of primary vitreous;** retrolental fibroplasia—2 entities, \*527  
 recent advances in ophthalmic surgery, 241  
 tissue culture of mouse lens epithelium, 488
- Leprosy;** year in Xiquipán leprosarium, 485
- Leukoma:** See under Cornea
- Lewis, P. M.:** Treatment of angioma of retina with diathermy, 503
- Lewisite:** See Gas, poisoning
- Lice:** See Pediculosis
- Light:** See also Infra-Red Rays  
 Adaptation: See Accommodation and Refraction  
 intraocular pressure of normal and glaucomatous eyes as affected by accessory light stimuli, 758  
 investigation in variable monochromatic light of outer vessels of eye, 101  
 qualitative and quantitative perimetry with monochromatic targets and with white targets of same luminous intensity, 240  
 sodium-vapor lamp and its use for refraction, 104
- Lighting;** responses to Ishihara test for color perception, \*20
- Limbus Conjunctivae:** See under Conjunctiva
- Corneae:** See Cornea
- Lupus erythematosus, acute disseminated, ocular changes in,** 235
- Lutman, F. C.:** Inheritance of arachnoidactyly, ectopia lentis and other congenital anomalies (Marfan's syndrome) in E. family, \*276
- Lyle, D. J.:** Changes in visual fields confirmed by pathologic diagnosis, 387  
 Ocular syndrome of cataract and papilledema in manifest form of parathyroid deficiency, 498
- Lymph Nodes;** virus studies in lymphomatoid diseases of ocular adnexa, 642
- Lymphatic System;** See also Lymph Nodes  
 capillary fragility and cutaneous lymphatic flow in relation to systemic and retinal vascular manifestations; rutin therapy, 649
- Lymphocytoma of orbit successfully treated by roentgen irradiation,** 106
- Lymphogranuloma, Hodgkin's:** See Hodgkin's Disease

- Pediculosis ciliaris; treatment with anticholinesterase agents; report of case, \*627
- Penicillin; contact lens electrode for iontophoresis, \*730
- experimental observations on intravitreal use of penicillin and other drugs, 357
- Therapy: See Eyes, injuries; Keratitis; Ophthalmia neonatorum; Thrombosis; etc.
- Penis; eruptive fever with involvement of respiratory tract, conjunctivitis, stomatitis and balanitis, 97
- Perception: See Color Perception
- Perimetry: See Vision
- Periphlebitis, retinal, 105
- retinae and its relation to primary tuberculous infection, 762
- Pharmacology and toxicology of cornea; contemporary concepts, \*253
- Phenylephrine Hydrochloride: See Neo-Synephrine
- Pheochromocytoma; changes in ocular fundus associated with pheochromocytoma of adrenal gland; report of 3 cases, 505
- Phlebitis: See also Periphlebitis; Thromboangiitis obliterans
- Phleboliths: See Veins, orbital
- Phorias; size of line in Maddox-rod test, 645
- treatment in adults, 647
- Phosphorus and Phosphorus Compounds; treatment of pediculosis ciliaris with anticholinesterase agents; report of case, \*627
- Physostigmine; treatment of pediculosis ciliaris with anticholinesterase agents; report of case, \*627
- Pigments; sight disturbances caused by proliferation of pigment epithelium, 763
- significance of intracutaneous test for hypersensitivity to uveal pigment, 364
- study of pigment cells of choroid in chick embryo, 95
- Pigmentation: See also Melanin; Xeroderma pigmentosum; etc.
- pigmentation of palpebral conjunctiva resulting from mascara, 356
- Pilocarpine; action on normal eyes, 492
- Pituitary Body, adenoma of, \*230
- ophthalmopathy of thyroepituitary origin, 508
- Pityrosporum Ovale: See Seborrhea
- Plasma: See Blood
- Plastic Surgery; integrated artificial eye and "vitallium" implants; further observations, 502, 760
- use of masseter, temporalis and frontalis muscles in correction of facial paralysis, 241
- Plessiotherapy: See Cornea
- Poisons and Poisoning: See under names of substances, as Gas; Methyl Alcohol; etc.
- Polioccephalitis: See Encephalitis
- Poliomyelitis, ocular symptoms of, 240
- Polynuritis: See Neuritis, multiple
- Posner, A.: Role of inheritance in glaucoma, \*125
- Postgraduate Education: See Education
- Pregnancy; acute retinopathy without hyperplasia in diabetic pregnancy, 492
- Premature Infants; blood groups and effects of roentgen irradiation in retrolental fibroplasia, \*659
- histopathologic aspects of retrolental fibroplasia, \*553
- persistence and hyperplasia of primary vitreous; retrolental fibroplasia—2 entities, \*527
- Pressure: See Blood, pressure; Tension
- Pringle-Bourneville's Disease: See Sclerosis, tuberosus
- Privine®; tolerance of contact lenses, 649
- Prizes: See Awards
- Propionates, use in ophthalmology, \*83
- Proptosis: See Exophthalmos
- Prosthesis: See under Eyes; Orbit
- Proteins in Blood: See Blood, proteins
- Provocative Tests: See Glaucoma
- Prowazek Bodies: See Trachoma
- Pseudoisochromatic Test: See Color Perception
- Pseudoxanthoma elasticum; Grönblad-Strandberg syndrome, with disciform degeneration of macula, 649
- elasticum; histologic findings in case of angiod streaks, 650
- Psychology of squinter, 101
- Pterygium, surgical treatment of, 233
- Ptosis: See Eyelids, ptosis
- Pupils; action of pilocarpine on normal eyes, 492
- clinical experiments with new ways of influencing intraocular tension; use of rutin to enhance tension-reducing effect of miotics by reducing permeability of blood-aqueous barrier, \*429
- mydriatics; clinical observation, \*42
- pupillometry; critique, 521
- tonic, produced by retrobulbar injection of alcohol, 760
- Radiations: See Radium; etc.
- Radioactivity: See also Radium; etc.
- studies of eye with radiosodium autographs, \*611
- Radiotherapy: See Eyelids
- Radium; beta radiation therapy, \*1
- Therapy: See under names of various diseases
- Radon, Therapy: See under names of various diseases, as Retinoblastoma; etc.
- Rathke's Pouch: See Pituitary Body
- Reading; comparison of eye conditions among 1,000 reading failures, 500 ophthalmic patients, and 150 unselected children, 642
- difficulty (dyslexia) from ophthalmic point of view, 642
- Recklinghausen's Disease: See Neurofibromatosis
- Recruits: See Military Medicine; etc.
- Reese, A. B.: Persistence and hyperplasia of primary vitreous; retrolental fibroplasia—2 entities, \*527
- Significance of base pressure in primary glaucoma, 515
- Reeve Prize awarded to J. C. McCulloch, 248
- Reflex, pupillary; tonic pupil produced by retrobulbar injection of alcohol, 760
- Refraction: See Accommodation and Refraction
- Respiratory Tract: See also Nasopharynx
- eruptive fever with involvement of respiratory tract, conjunctivitis, stomatitis and balanitis, 97
- Reticuloendothelial System; Mikulicz's disease and syndrome, 512, 757
- Retina: See also Macula Lutea
- acute retinopathy without hyperplasia in diabetic pregnancy, 492
- angiomatosis in infant, 244
- Blood Supply: See also Thrombosis; etc.
- blood supply; capillary fragility and cutaneous lymphatic flow in relation to systemic and retinal vascular manifestations; rutin therapy, 649
- blood supply; experimental hypertensive retinopathy, 234
- blood supply; Grönblad-Strandberg syndrome, with disciform degeneration of macula, 649
- blood supply; histologic findings in case of angiod streaks, 650
- blood supply; new method of measuring retinal blood pressure as objective proof of formula of hydrodynamic equilibrium of eye, 639
- blood supply; pressure in central retinal artery, 367
- blood supply; retinal arteriovenous index, 493
- blood supply; retinal arteries or arterioles, 481
- blood supply; retinal periphlebitis, 105
- blood supply; treatment of certain vascular disturbances of eye with retrobulbar injection of nicotinic acid, 494
- changes in ocular fundus associated with pheochromocytoma of adrenal gland; report of 3 cases, 505
- changes with acute reduction of vision as initial symptoms of infectious mononucleosis, 762

## Neuritis—Continued

- optic; allergic ocular reaction to tuberculin test; bilateral cyclitis and neuroretinitis; \*436  
 optic, and oculomotor paralysis, 102  
 optic; fundus in fresh gunshot wounds of skull, 100  
 optic, ocular syndrome of cataract and papilledema in manifest form of parathyroid deficiency, 498  
 retrobulbar, prognosis of, 761  
 Neuroblastoma, intraorbital, \*229  
 of adrenals with orbital metastases, 105  
 Neurofibroma; neural and meningeal tumors, \*215  
 Neurofibromatosis associated with tumors of optic papilla; report of case, \*718  
 Neurofibrosarcoma; intraorbital tumors, \*223  
 Neurology: See also Nerves; Nervous System; etc.  
 practice in United States, 377  
 present trends in practice of, 378  
 Neuroma; neurofibromatosis associated with tumors of optic papilla; report of case, \*718  
 Neuroretinitis: See Neuritis, optic; Retinitis  
 Newborn Infants; apparent blindness; gray pseudopterygia of optic nerve, 243  
 penicillin as prophylactic against, ophthalmia neonatorum; comprehensive study, \*444  
 pseudosinusitis of newborn and young infant, 102  
 Nicotinic Acid, treatment of certain vascular disturbances of eye with retrobulbar injection of, 494  
 Nikethamide; studies of effect of certain stimulants on accommodation of eye and of threshold value for effect of vitamin B<sub>1</sub> on accommodation, 355  
 Nitrocompounds; acute reversible cataract in chicken due to various nitrocompounds, 483  
 Nitrogen Mustard: See Chloroethylamines  
 Nolasco, J. B.: Responses to Ishihara test for color perception, \*20  
 Nomenclature; traumatic choroiditis; review of literature and report of 10 cases, \*341  
 Nylon Sutures: See Sutures  
 Nystagmus; character of nystagmus induced by amytal in chronic alcoholics, 490  
 pathogenesis and pathophysiology of coal miner's nystagmus, 241  
 Oaks, L. W.: Divergence insufficiency as practical problem, \*562

## OBITUARIES:

Weeks, John Elmer, 752

- Occipital Lobes: See Brain  
 Occupational Diseases: See Industrial Diseases  
 O'Conner Clinch Operation: See Strabismus  
 Onchocercosis; chronic superficial punctate keratitis caused by onchocerci volvulus, 647  
 Ophthalmia: See also Conjunctivitis; Eyes, diseases  
 Egyptian: See Trachoma  
 Gonorrheal: See Gonorrhea  
 neonatorum, penicillin as prophylactic against; comprehensive study, \*444  
 sympathetic; significance of intracutaneous test for hypersensitivity to uveal pigment, 364

## OPHTHALMOLOGIC REVIEWS:

- Intraorbital tumors; A. W. Forest, \*198  
 Metabolism of cornea; T. D. Duane, \*736  
 Ophthalmologic societies, directory of, 111  
 Ophthalmology, American Board of, 246, 354  
 and aviation, 358, 484  
 history; early photograph of von Helmholtz with explanatory letter, \*570  
 industrial, as of 1946, 369  
 Institute of Ophthalmology, London, 523  
 ophthalmology's postwar responsibilities and opportunities (chairman's address), 369  
 Teaching: See under Education  
 Ophthalmopathy: See Eyes, diseases

Ophthalmoplegia: See Paralysis

Ophthalmoscopy: See Eyes, examination; Glaucoma

Ophthalmotonometry: See Tension

Optic Chiasm, toxic disorders of, 364

Optic Disk; Optic Papilla: See Nerves, optic; Neuritis, optic

Thalamus: See Thalamus

Tract: See Nerves, optic

Optics; supposed torsion of eye around visual axis in oblique directions of gaze, \*704

Orbit, carcinoma of, \*227

chondrosarcoma of, 651  
 exophthalmos with intermittent aggravation; special form of variable exophthalmos, 242

granular cell myoblastoma of; report of

2 cases, 498

hydatid of, 647

intraorbital tumors, \*198

lymphocytoma successfully treated by roentgen irradiation, 106

motor block of extraocular muscles by deep orbital injection, \*5

neuroblastoma of adrenals with orbital metastases, 105

sympathicoblastomas with metastases to, 763

tonic pupil produced by retrobulbar injection of alcohol, 760

tumors, exophthalmos in relation to; report of 8 cases, 102

tumors of vascular origin, \*204

use of buccal mucosa in restoration of orbital socket, 511

Orthoptics: See also Strabismus

American Orthoptic Council, 637

annual examination for orthoptic technicians, 354

Barbara Gregg Ingalls Orthoptic Clinic, 524

place of peripheral fusion in, 102

problems in research in, 647

psychology of squinter, 101

School of Orthoptics, Massachusetts Eye and Ear Infirmary, 246

which squints respond best to orthoptic treatment? 101

Osteitis deformans; glaucoma secondary to fibrocystic disease of bone, 644

Osteomyelitis; pseudosinusitis of newborn and young infant, 102

Osteosarcoma, metastatic, in choroid, 494

Oxazolidinediones; visual effects of tridione, 242

Oxygen; metabolism of cornea, \*736

some researches on respiration of cornea in albino rats, 234

Paget's Disease of Bones: See Osteitis deformans

Palsy: See Paralysis

Pannus: See Trachoma

Panophthalmitis: See Ophthalmia

Papilledema: See Neuritis, optic

Paracentesis: See Eyes, surgery

Paraganglioma; pseudostellate retinopathy in patient with paraganglioma, 367

Paralysis: See also Poliomyelitis

Bell's: See Paralysis, facial

congenital syndrome of retraction of globe (new variety), 491

facial, use of masseter, temporalis and frontalis muscles in correction of, 241

Infantile: See Poliomyelitis

optic neuritis and oculomotor paralysis, 102

Parasympathomimetic Agents: See Nervous System

Parathyroid; ocular syndrome of cataract and papilledema in manifest form of parathyroid deficiency, 498

Paratrachoma: See Conjunctivitis

Paredrine hydrobromide; mydriatics; clinical observation, \*53

Parietal Lobe: See Brain

Parinaud-Motais Operation: See Eyelids, ptosis

Parotitis; ocular manifestations of mumps, 235

Pascal, J. I.: Muscle schemas, 245

Paul, T. O.: Blood groups and effects of roentgen irradiation in retrolental fibroplasia, \*659

## Societies—Continued

- Royal Australasian College of Surgeons, 750  
 sectional, directory of, 115  
 sixteenth International Congress of Ophthalmology, 353  
 Sociedad Nicaragiense de oftalmología, 354  
 state, directory of, 117

## SOCIETY TRANSACTIONS:

- American Medical Association, Section on Ophthalmology, 369  
 American Ophthalmological Society, 496
- Sodium, propionates; use of propionates in ophthalmology, \*83  
 Radioactivity: See Radioactivity  
 studies of physiology of eye using tracer substances; steady-state ratio of sodium between plasma and aqueous humor in guinea pig, 103  
 vapor lamp and its use for refraction, 104
- Soldiers: See Military Medicine  
 Solid Carbon Dioxide: See Cornea
- Souders, B. F.: Juxtapapillary hemangio-endothelioma of retina; report of case, \*178
- Spectacles: See Glasses  
 Spinal Fluid: See Cerebrospinal Fluid  
 Squint: See Strabismus
- Staphylococci; antitoxin treatment of staphylococcal corneal ulceration, 96
- Stenosis: See Lacrimal Organs
- Stereo-Ophthalmoscopy: See Eyes, examination
- Stevens-Johnson Disease: See Erythema multiforme
- Stocker, F. W.: Clinical experiments with new ways of influencing intraocular tension; use of rutin to enhance tension-reducing effect of miotics by reducing permeability of blood-aqueous barrier, \*429
- Stomatitis; eruptive fever with involvement of respiratory tract, conjunctivitis, stomatitis and balanitis, 97
- Strabismus; anatomic factors in etiology of heterotropia, 760  
 divergence insufficiency as practical problem, \*562  
 muscle schemas, 245  
 concomitant, nonoperative treatment of, 365  
 progressive muscular dystrophy involving extraocular muscles; report of case, \*334  
 psychology of squinter, 101  
 surgical approach to inferior oblique muscle, \*607  
 surgical correction of paresis of superior oblique, 490  
 symposium on, 353  
 technic for muscle resection without use of Prince forceps, 760  
 undercorrection and overcorrection by myo-campimetry, 365  
 vergence test; evaluation of various techniques, 646  
 voluntary dissociation of accommodation and convergence faculty; 2 observations, \*599  
 which squints respond best of orthoptic treatment? 101
- Strandberg-Grönblad Syndrome: See Pseudo-xanthoma elasticum; Retina, blood supply
- Streptomycin, intravitreal use of, \*629
- Intravitreal; its toxicity and diffusion, 648
- Sturm's Interval: See Astigmatism
- Sulfonamides, Therapy: See Eyes, diseases; etc.
- Suprarenals: See Adrenals
- Surgery: See also Apparatus; Instruments; Sutures; and under names of organs and diseases, as Cataract; Cornea; Eyelids; Eyes; Glaucoma; etc.  
 Plastic: See Plastic Surgery  
 Sutures: See also Cataract, extraction; etc.  
 nylon thread in ocular surgery, 241  
 technic of application in dacryocystorhinostomy, 362

- Swan, K. C.: Pharmacology and toxicology of cornea; contemporary concept, \*253
- Sympathicoblastomas with metastases to orbit, 763
- Symposium on strabismus, 353
- Synchysis: See Vitreous Humor
- Syntropan; mydriatics; clinical observation, \*51
- Syphilis; corneal changes during treatment with arsphenamine, 641
- Tarsectomy: See under Eyelids
- Teaching: See Ophthalmology
- Technicians: See Orthoptics
- Temporomaxillary Joint: See Jaws
- Tenotomy: See Glaucoma
- Tension: See also Glaucoma  
 clinical experiments with new ways of influencing intraocular tension; use of rutin to enhance tension-reducing effect of miotics by reducing permeability of blood-aqueous barrier, \*429  
 falling dogma; ocular hypertension in glaucoma, 759  
 further gonioscopic studies on canal of Schlemm, \*393  
 influence of local arterial blood pressure on aqueous humor and intraocular pressure; experimental study of mechanisms maintaining intraocular pressure, 97  
 intraocular pressure of normal and glaucomatous eyes as affected by accessory light stimuli, 758  
 new method of measuring retinal blood pressure as objective proof of formula of hydrodynamic equilibrium of eye, 639  
 ophthalmotonometry, 491  
 problems in calibration of tonometers, 520, 645  
 significance of base pressure in primary glaucoma, 515  
 studies on outflow pressure of aqueous in human beings, 103
- Testes; choroidal metastasis of testicular chorionic epithelioma; report of case, \*587
- Tetralol: See Naphthalene
- Thalamus and glaucoma, 360
- Theodore, F. H.: Use of propionates in ophthalmology; preliminary report, \*83
- Thiamine Hydrochloride; studies on effect of certain stimulants on accommodation of eye and of threshold value for effect of vitamin B<sub>1</sub> on accommodation, 355
- Thromboangiitis obliterans; condition of ocular vessels in endarteritis obliterans (Winiwarter-Buerger), 485
- Thrombosis; treatment of thrombosis of cavernous sinus with intra-arterial injections of penicillin, 365
- Thygeson, P.: Clinical signs of diagnostic importance in conjunctivitis, 370
- Thyroid: See also Goiter  
 ophthalmopathy of thyropituitary origin, 508
- Tissue: See also Cells  
 cultures of mouse lens epithelium, 488  
 electrometric variations in tissue pH in trachoma, 105  
 research and cell culture of cornea, 757  
 respiration; cyanide inhibition of corneal respiration, 640  
 respiration; metabolism of cornea, \*736  
 some researches on respiration of cornea in albino rats, 234  
 therapy of ocular complications in patients with hypertension, 108  
 therapy of traumatic changes of vitreous in period of World War II, 108  
 therapy; treatment of retinitis pigmentosa with reference to Filatov method, 104
- Tonometers: See also Tension  
 problems in calibration of, 520, 645
- Tonometry: See Tension
- Tower, P.: Contact lens electrode for iontophoresis, \*730  
 Traumatic choroiditis; review of literature and report of 10 cases, \*341
- Toxicology and pharmacology of cornea; contemporary concepts, \*253
- Trachoma; Denig's operation for trachomatous pannus, 493  
 electrometric variations in tissue pH in, 105

- Retina**—Continued  
 chronic glaucoma and minimal elective vasodilatation, 361  
 detachment, and intracapsular cataract extraction, 362  
 detachment, modifications in critical frequency of fusion after surgical repair of, 650  
 detachment; recovery of visual functions following surgical treatment, 492  
 detachment; surgical cure with perforation of macula; report of case, 243  
 hemorrhage, capillary fragility and capillary permeability in relation to, 242  
 hemorrhage; successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, 503  
 Inflammation: See Retinitis  
 inheritance of retinoblastoma; 2 families supplying evidence, 376  
 juxtapapillary hemangioid endothelioma of; report of case, \*178  
 mechanism of production of massive pre-retinal hemorrhage following rupture of congenital medial-defect intracranial aneurysm, 364  
 peripherebittis retinae and its relation to primary tuberculous infection, 762  
 pseudostellate retinopathy in patient with paraganglioma, 367  
 retinoblastoma (retinal glioma) cured by radon seeds; report of case, \*32  
 scleroderma and lesions in fundus, 643  
 softening in sectors and detachment, 243  
 tissue therapy of ocular complications in patients with hypertension, 108  
 treatment of anglioma with diathermy, 503  
 tuberosus sclerosis in 3 siblings, \*473  
**Retinitis**; allergic ocular reaction to tuberculin test; bilateral cyclitis and neuroretinitis, \*436  
 clinical forms of tuberculosis of macula, 366  
 ocular changes in acute disseminated lupus erythematosus, 235  
 pigmentosa; pathogenesis of pigmentary degeneration, 493  
 pigmentosa, present state of problem of, 761  
 pigmentosa; treatment with reference to Filatov method, 104  
 pigmentosa with reference to otologic, neurologic and endocrine complications, 762  
 proliferans and tuberculosis, 104  
 proliferans; successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, 503  
**Retinoblastoma**, diagnosis of, 513  
 inheritance of; 2 families supplying evidence, 376  
 intraocular, \*230  
 retinal glioma cured by radon seeds; report of case, \*32  
**Retinopathy**: See under Retina  
**Retinoscopy**: See under Retina  
**Rheumatism**; nodular rheumatic episcleritis, 756  
**Rhinopharynx**: See Nasopharynx  
**Riboflavin**; acute ocular manifestations of ariboflavinosis, 643  
 flare-up of trachomatous pannus due to ariboflavinosis, 493  
**Richardson, S.**: Diffuse malignant melanoma of iris; report of cases, 518  
**Rickettsia**; rickettsial bodies in epidemic nummular conjunctivitis (epidemic keratoconjunctivitis), 356  
**Rodit, D.**: Responses to Ishihara test for color perception, \*20  
**Roentgen Rays**, Therapy: See under names of organs, regions and diseases, as Lens, Crystalline; Lymphocytoma; etc.  
**Rosen, E.**: Interstitial keratitis and vestibulo-auditory symptoms following vaccination, \*24  
**Ruedemann, A. D.**: Beta radiation therapy, \*1  
 Blood protein in certain types of changes in lens, 516  
**Rupp, C. Jr.**: Present trends in practice of neurology, 378  
**Rutin**: See Capillaries; Flavones  
**Sacks-Wilner, A.**: Penicillin as prophylactic against ophthalmia neonatorum; comprehensive study, \*444  
**Sacks-Wilner, E. P.**: Penicillin as prophylactic against ophthalmia neonatorum; comprehensive study, \*444  
**von Sallmann, L.**: Studies of eye with radio-sodium autographs, \*611  
**Sarcoidosis**, Boeck's; differential diagnosis; report of 10 cases with ocular involvement, \*667  
**Sarcoma**: See Cancer; Chondrosarcoma; Myxosarcoma; Neurofibrosarcoma; Osteosarcoma; Tumors; etc.  
**Schaumann's Disease**: See Sarcoidosis  
**Schizophrenia**: See Dementia Precox  
**Schlemm's Canal**: See under Eyes  
**Schlossman, A.**: Role of inheritance in glaucoma, \*125  
**Schneider, R.**: Blood protein in certain types of changes in lens, 516  
**Sclera**; development of ectodermal framework of optic nerve, with reference to glial lamina cribrosa, 481  
 nodular rheumatic episcleritis, 756  
 recent advances in ophthalmic surgery, 241  
 scleromalacia perforans; report of case, \*183  
 Surgery: See also under Cataract; Glaucoma surgery; treatment of perforated corneal ulcer by autoplasmic scleral transplantation, 233  
**Scleroderma** and lesions in fundus, 643  
**Sclerosis**: See also Arteriosclerosis tuberosus, in 3 siblings, \*473  
**Scotoma**; widening of angioscotoma in alarm reaction, 764  
**Scrofula**: See Tuberculosis  
**Seborrhea**; Pityrosporum ovale in seborrheic blepharitis and conjunctivitis, 489  
**Secretions**, Internal: See Endocrine Glands  
**Sensitization**: See Anaphylaxis and Allergy  
**Shannon, C. E. G.**: Ophthalmopathy of hypopituitary origin, 508  
 Retinoblastoma (retinal glioma) cured by radon seeds; report of case, \*32  
**Shoemaker, R. E.**: Intravitreal use of streptomycin, \*629  
**Sinus**, Thrombosis: See Thrombosis  
**Sjögren Syndrome**: See Keratoconjunctivitis  
**Skin**, diseases; relation of cutaneous diseases and ocular lesions, 98  
 grave manifestations of gold therapy in cornea and skin, 96  
**Skull**: See Cranium  
**Sleep** with half-open eyes (physiologic lagophthalmus), 489  
**Smallpox**; interstitial keratitis and vestibulo-auditory symptoms following vaccination, \*24  
 new concepts concerning ocular complications following vaccination, 643  
**Societies**, Alabama Academy of Ophthalmology and Otolaryngology, 751  
 Association for Prevention of Blindness (Mexico), 751  
 Association for Research in Ophthalmology, 247, 248, 751  
 foreign, directory of, 111  
 Georgia Society of Ophthalmology and Otolaryngology, 248  
 International, directory of, 111  
 local, directory of, 119  
 Medical Society of State of New York, Section on Ophthalmology, 638  
 Midwestern Section of Association for Research in Ophthalmology, 750  
 national, directory of, 115  
 ophthalmologic, directory of, 111  
 Ophthalmological Society of Australia, 247, 638  
 Ophthalmological Society of Egypt, 248  
 Ophthalmological Society of United Kingdom, annual congress, 637  
 Oregon Academy Postgraduate Convention in Ophthalmology and Otolaryngology, 750  
 Oxford Ophthalmological Congress, 638  
 Pennsylvania Academy of Ophthalmology and Otolaryngology, 354

# ARCHIVES OF OPHTHALMOLOGY

Continuing the Publication  
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VOLUME 41  
1949

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO 10, ILL.



## Trachoma—Continued

- federal campaign against, 338
- flare-up of trachomatous pannus due to ariboflavinosis, 493
- new and fast method to demonstrate trachoma inclusion bodies, 489
- pannus follicularis trachomatous, 96
- Transplantation: See under Cornea; Skin; Vitreous Humor; etc.
- Triching: See Glaucoma
- Tridione: See Oxazolidinediones
- Tuberculosis: See also under special structures of eye and names of diseases, as Macula Lutea
  - allergic ocular reaction to tuberculin test; bilateral cyclitis and neuroretinitis, \*436
  - and retinitis proliferans, 104
  - differential diagnosis of Boeck's sarcoidosis; report of 10 cases with ocular involvement, \*667
  - grave manifestations of gold therapy in cornea and skin, 96
  - periphlebitis retinae and its relation to primary tuberculous infection, 762
- Tumors: See also Adenoma; Angioma; Glioma; Melanoma; Myoblastoma; Neuroblastoma; Neurofibroma; Neuroma; Retinoblastoma; etc.; and under names of organs and regions, as Eyes; Lacrimal Organs; Orbit; etc.
  - mixed, of lacrimal gland, \*210
  - pigmented, 105
- Tyndall Phenomenon in anterior chamber, 355

## Ulcers, Corneal: See Cornea, ulcers

## Ultrashort Waves: See under names of organs, regions and diseases

## Ultraviolet Rays: See Light

- Uvea, Inflammation: See also Iridocyclitis; Ophthalmia, sympathetic
  - inflammation; Vogt-Koyanagi syndrome, 651
  - significance of intracutaneous test for hypersensitivity to uveal pigment, 364
- Uveitis: See Uvea, inflammation

## Vaccinia: See Smallpox

## Vasomotor System: See also Arteries; Blood, pressure; Blood vessels; Capillaries; Veins

## chronic glaucoma and minimal elective vasodilatation, 361

## Veins: See also Thrombosis; Vasomotor System; etc.

## diagnosis and treatment of varix of angular vein, 481

## orbital; exophthalmos with intermittent aggravation; special form of variable exophthalmos, 242

## Verhoeff, F. H.: Successful diathermy treatment of recurring retinal hemorrhage and retinitis proliferans; report of case, 503

## Vertigo; interstitial keratitis and vestibulo-auditory symptoms following vaccination, \*24

## Vestibular Apparatus: See Ear

## Viruses; experimental studies of inclusion blennorrhoea; isolation of virus, \*151

## virus studies in lymphomatoid diseases of ocular adnexa, 642

## Vision: See also Accommodation and Refraction; Blindness; etc.

## binocular, 106

## bitemporal visual field defect in aqueduct stenosis, 764

## changes in visual fields confirmed by pathologic diagnosis, 387

## effect of visual training on existing myopia, 104

## effects of diabetes on cataract and on vision, \*462

## modifications in critical frequency of fusion after surgical repair of detachment of retina, 650

## peripheral and central disturbances of visual fields; aspect of di-opthalmology, 244

## Vision—Continued

## physiology; supposed torsion of eye around visual axis in oblique directions of gaze, \*704

## place of peripheral fusion in orthoptics, 102

## qualitative and quantitative perimetry with monochromatic targets and with white targets of same luminous intensity, 240

## recovery of visual functions following surgical treatment of retinal detachment, 492

## retinal changes with acute reduction of vision as initial symptoms of infectious mononucleosis, 762

## simple, self-registering perimeter, 645

## simplified perimeter of wall type, \*633

## Tests: See also Accommodation and Refraction; Color Perception

## tests; modified 3 character test for binocular vision especially applicable to examination of amblyopic children, \*460

## toxic disorders of chiasm, 364

## visual effects of tridione, 242

## Vitalium: See Metals

## Vitamins: See Nicotinic Acid; Riboflavin; Thiamine; etc.

B<sub>1</sub>: See Thiamine HydrochlorideB<sub>2</sub>: See Riboflavin

## P: See Flavones

## P-P: See Nicotinic Acid

## Vitreous Humor, cyst, congenital; report of case, \*734

## experimental observations on intravitreal use of penicillin and other drugs, 357

## extraction of cataract in presence of fluid vitreous (synchysis), 499

## histopathologic aspects of retrolental fibroplasia, \*553

## intravitreal use of streptomycin, \*629

## intravitreal streptomycin; its toxicity and diffusion, 648

## motor block of extraocular muscles by deep orbital injection, \*5

## operative technic of vitreous replacement, 107

## persistence and hyperplasia of primary vitreous; retrolental fibroplasia—2 entities, \*527

## slight disturbances caused by proliferation of pigment epithelium, 763

## tissue therapy of traumatic changes of vitreous in period of World War II, 108

## transplantation; preliminary report, 107

## Waldman, J.: Retinoblastoma (retinal glioma) cured by radon seeds; report of case, \*32

## War: See also Military Medicine; etc.

## ophthalmology's postwar responsibilities and opportunities (chairman's address), 369

## Wecker's Sign: See Scotoma

## Weizenblatt, S.: Allergic ocular reaction to tuberculin test; bilateral cyclitis and neuroretinitis, \*436

## Wheeler, M. C.: Discoloration of eyelids from yellow mercuric oxide, 496

## Wilson, G.: Present trends in practice of neurology, 378

## Winiwarter-Buerger Disease: See Thromboangiitis obliterans

## Word Blindness: See Aphasia

## Wounds: See also Military Medicine; War; and under organs and regions

## indirect gunshot injury of eye simulating Elliot's trephining operation, 239

## healing, morphologic changes in cells of corneal epithelium in, \*306

## stimulation of corneal epithelization with topical application of erythrocytes, 640

## Xanthelasma and autonomic nervous system; new syndrome, 236

## Xeroderma pigmentosum with affection of eye, 757

# CONTENTS OF VOLUME 41

## JANUARY 1949. NUMBER 1

	PAGE
Beta Radiation Therapy. A. D. Ruedemann, M.D., Detroit.....	1
Motor Block of Extraocular Muscles by Deep Orbital Injection. Harold Gifford Jr., M.D., Omaha.....	5
Responses to the Ishihara Test for Color Perception. J. B. Nolasco, M.D., Manila, Philippines, and Deogracias Rodil, M.D., Champaign, Ill.....	20
Interstitial Keratitis and Vestibuloauditory Symptoms Following Vaccination. Emanuel Rosen, M.D., Newark, N. J.....	24
Retinoblastoma (Retinal Glioma) Cured by Radon Seeds: Report of a Case. Joseph Waldman, M.D., and C. E. G. Shannon, M.D., Philadelphia.....	32
Mydriatics: A Clinical Observation. J. B. Feldman, M.D., Philadelphia.....	42
Malignant Retrobulbar Neuritis. Adalbert Fuchs, M.D., Shanghai, China....	60
Technic of Goniotomy for Congenital Glaucoma. Otto Barkan, M.D., San Francisco .....	65
Use of Propionates in Ophthalmology: A Preliminary Report. Frederick H. Theodore, M.D., New York.....	83
Abstracts from Current Literature.....	95
Book Reviews.....	109
Directory of Ophthalmologic Societies.....	111

## FEBRUARY 1949. NUMBER 2

Role of Inheritance in Glaucoma. Adolph Posner, M.D., and Abraham Schlossman, M.D., New York.....	125
Experimental Studies of Inclusion Blennorrhoea: Isolation of a Virus. Alson E. Braley, M.D., New York.....	151
Use of Phenylephrine Hydrochloride (Neo-Synephrine Hydrochloride®) in Ophthalmology. Parker Heath, M.D., Boston, and C. W. Geiter, M.D., North Kansas City, Mo.....	172
Juxtapapillary Hemangioendothelioma of the Retina: Report of a Case. Benjamin F. Souders, M.D., Sc.D. (Med.), Reading, Pa.....	178
Scleromalacia Perforans: Report of a Case. Melvin Harbater, M.D., Manhasset, N. Y.....	183



APRIL—*Continued*

PAGE

Clinical Experiments with New Ways of Influencing the Intraocular Tension: II. Use of Rutin to Enhance the Tension-Reducing Effect of Miotics by Reducing the Permeability of the Blood-Aqueous Barrier. Frederick W. Stocker, M.D., Durham, N. C.....	429
Allergic Ocular Reaction to the Tuberculin Test: Bilateral Cyclitis and Neuro- retinitis. S. Weizenblatt, M.D., Asheville, N. C.....	436
Penicillin as a Prophylactic Against Ophthalmia Neonatorum: A Comprehen- sive Study. Arthur Sacks-Wilner, M.D., and Erwin P. Sacks-Wilner, M.D., Trenton, N. J.....	444
Cataract in Dystrophia Myotonica. David N. Farber, M.D., Reading, Pa....	450
Modified Three Character Test for Binocular Vision, Especially Applicable to the Examination of Amblyopic Children. Conrad Berens, M.D., New York.....	460
Effects of Diabetes on Cataract and on Vision. Benjamin Lee Gordon, M.D., Atlantic City, N. J.....	462
Tuberous Sclerosis in Three Siblings. Paul W. Miles, M.D., and Joseph M. Dixon, M.D., St. Louis.....	473
Abstracts from Current Literature.....	481
Society Transactions: American Ophthalmological Society.....	496
News and Notes.....	523
Book Reviews.....	525

## MAY 1949. NUMBER 5

V

Persistence and Hyperplasia of Primary Vitreous: Retrolental Fibroplasia— Two Entities. Algernon B. Reese, M.D., New York.....	527
Histopathologic Aspects of Retrolental Fibroplasia. Bertha A. Klien, M.D., Chicago .....	553
Divergence Insufficiency as a Practical Problem. L. Weston Oaks, M.D., Provo, Utah.....	562
An Early Photograph of von Helmholtz with Explanatory Letter. Joseph C. Aub, M.D., Boston.....	570
Production of Cataract in Rats by Beta-Tetralol and Other Derivatives of Naphthalene. O. Garth Fitzhugh, Ph.D., Washington, D. C., and Wilhelm H. Buschke, M.D., Baltimore.....	572
Use of Antihistaminic Drugs in Control of Atropine Dermatitis and Conjunc- tivitis. F. Bruce Fralick, M.D., and Robert D. Kiess, M.D., Ann Arbor, Mich. ....	583
Choroidal Metastasis of a Testicular Chorionic Epithelioma: Report of a Case. George K. Kambara, M.D., Los Angeles.....	587

FEBRUARY—*Continued*

	PAGE
Congenital Ptosis: A Classification of Two Hundred Cases. Raynold N. Berke, M.D., Hackensack, N. J.....	188
Ophthalmologic Review:	
Intraorbital Tumors. Arnold W. Forrest, M.D., New York.....	198
Abstracts from Current Literature.....	233
Correspondence:	
Muscle Schemas. Joseph I. Pascal, M.D., New York.....	245
News and Notes.....	246
Book Reviews.....	249

## MARCH 1949. NUMBER 3

Pharmacology and Toxicology of the Cornea: Contemporary Concepts. Kenneth C. Swan, M.D., Portland, Ore.....	253
Inheritance of Arachnodactyly, Ectopia Lentis and Other Congenital Anomalies (Marfan's Syndrome) in the E. Family. Frank C. Lutman, M.D., Philadelphia, and James V. Neel, M.D., Ph.D., Ann Arbor, Mich.....	276
Morphologic Changes in Cells of Corneal Epithelium in Wound Healing. Wilhelm Buschke, M.D., New York.....	306
Myxosarcoma of the Eyelid. Walter Moehle, M.D., Brooklyn.....	317
Motais-Parinaud Type of Operation for Ptosis: Report on Thirty-Five Cases. Raynold N. Berke, M.D., Hackensack, N. J.....	324
Progressive Muscular Dystrophy Involving the Extraocular Muscles: Report of a Case. Samuel Gartner, M.D., and Edwin Billet, M.D., New York..	334
Traumatic Choroiditis: Review of Literature and Report of Ten Cases. Paul Tower, M.D., Los Angeles.....	341
News and Notes.....	353
Abstracts from Current Literature.....	355
Society Transactions:	
American Medical Association, Section on Ophthalmology.....	369
Book Reviews.....	390

## APRIL 1949. NUMBER 4

Further Gonioscopic Studies on the Canal of Schlemm. Peter C. Kronfeld, M.D., Chicago.....	393
Vascularization of the Cornea: Its Experimental Induction by Small Lesions and a New Theory of Its Pathogenesis. David G. Cogan, M.D., Boston..	406
Diathermy Cauterization of the Ciliary Body for Glaucoma. Samuel J. Meyer, M.D., Chicago.....	417

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JUNE 1949

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH  
DEARBORN STREET, CHICAGO 10, ILLINOIS. ANNUAL SUBSCRIPTION, \$10.00

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Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago,  
Under the Act of Congress of March 3, 1879

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## MAY—Continued

	PAGE
Voluntary Dissociation of the Accommodation and the Convergence Faculty: Two Observations. C. Keith Barnes, M.D., Fort Worth, Texas.....	599
A Surgical Approach to the Inferior Oblique Muscle. Walter F. Johnson, M.D., New York.....	607
Studies of the Eye with Radiosodium Autographs. Ludwig von Sallmann, M.D.; Titus C. Evans, Ph.D., and Beatrice Dillon, M.A., New York....	611
Treatment of Pediculosis Ciliaris with Anticholinesterase Agents: Report of a Case. David G. Cogan, M.D., and W. Morton Grant, M.D., Boston....	627
Intravitreal Use of Streptomycin. Robert E. Shoemaker, M.D., Allentown, Pa.	629
Clinical Notes:	
A Simplified Perimeter of Wall Type. Anthony Ambrose, M.D., Newark, N. J. ....	633
News and Notes.....	637
Abstracts from Current Literature.....	639
Book Reviews.....	653

## JUNE 1949. NUMBER 6

Blood Groups and Effects of Roentgen Irradiation in Retroental Fibroplasia. Thomas O. Paul, M.D., Birmingham, Ala.....	659
Differential Diagnosis of Boeck's Sarcoidosis: Report of Ten Cases with Ocular Involvement. Byron L. Gifford, M.D., and Arlington C. Krause, M.D., Chicago .....	667
Ocular Findings in Three Hundred and Twenty-Three Patients with Schizo- phrenia: A Preliminary Report. Martin Cohen, M.D., New York.....	697
Reserve Accommodation. Harry Eggers, M.D., New York.....	701
Supposed Torsion of the Eye Around the Visual Axis in Oblique Directions of Gaze. Prof. M. Márquez, M.D., México, D. F., Mexico.....	704
Neurofibromatosis Associated with Tumors of the Optic Papilla: Report of a Case. J. Goldsmith, M.D., New York.....	718
Contact Lens Electrode for Iontophoresis. Paul Tower, M.D., Los Angeles....	730
Congenital Cyst of the Vitreous: Report of a Case. J. V. Cassady, M.D., South Bend, Ind.....	734
Ophthalmologic Reviews:	
Metabolism of the Cornea. T. D. Duane, M.D., Iowa City.....	736
News and Notes.....	750
Obituaries:	
John Elmer Weeks, M.D.....	752
Abstracts from Current Literature.....	755
Book Reviews .....	765
General Index .....	767